MBBC 2024
Grand Final

Additional Learning Resource (IBB):

Neurological Disorders

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Neurology

Neurological problems can be caused by infections, neurodegenerative disorders, trauma, congenital defects, vascular problems, and tumors. This section is an introduction to neurological diagnosis and the main features of important neurological conditions.

Neurological Diagnosis

The first step in medical diagnosis is always a good history, looking at the patient's current problems, previous medical history, risk factors, family history, and use of medications. The medical history is followed by a clinical examination to gather information on functions of the brain and spinal cord, including the following:

- cranial nerve functions
- motor functions and reflexes
- skin sensation
- coordination
- psychological states

Sometimes a diagnosis is already evident after these two examination steps. However, further special tests are usually carried out to confirm the diagnosis or exclude similar diseases. These tests may include imaging methods (CT and MRI), electroencephalography (EEG), electromyography (EMG), nerve conduction studies, lumbar puncture (spinal tap), blood tests, and biopsy. These tests will be described in a little more detail later.

Signs and symptoms of neurological conditions

Our nervous system is at least partially involved in almost all regulatory processes of our body. Accordingly, functional deficits can also lead to a variety of symptoms. In the following, we would like to present essential neurological symptoms, divided into four major areas: motor function, sensory function, cognition, and others.
Unfortunately, a precise classification of the symptoms, and especially their causes, is not always possible. For example, stance or gait problems can have motor and/or sensory causes.
More generally, identical symptoms can be triggered by various causes.
For example, damage to the speech center can be caused by a stroke or a nearby tumor. However, both cases result in a disturbance of speech. The physical examination cannot differentiate between these two cases. Still, it provides crucial conclusions about the location of a problem in the brain and enables specific further tests to be carried out in these areas.
On the other hand, identical causes can also lead to different symptoms. For example, a stroke can trigger a wide variety of symptoms depending on the brain area in which it occurs.

Motor Signs

The most significant elements of the examination of motor functions are:

- detection of paresis or paralysis
- changes in muscle tone and reflexes
- abnormal spontaneous movements

Paralysis

It is important to distinguish between central paralysis (impairment of the corticospinal tract neurons) and peripheral paralysis (impairment of the motor neuron).
Damage to the corticospinal tract neurons is usually associated with spastic paralysis, in which loss of fine motor skills is associated with increased muscle tone (spastic tone) and exaggerated reflexes.
When motor neurons are damaged, flaccid paralysis occurs. This type of paralysis is characterized by loss or reduction in muscle strength, loss of muscle tone (flaccidity), loss of reflexes, and loss of the paralyzed muscles' mass.

Spastic paralysis

Spastic paralysis occurs after major central nervous system damage, such as after a stroke. In spastic paralysis, the main structures affected are the corticospinal tract and parts of the basal ganglia – the corticospinal damage causes the paralysis, and the associated basal ganglia damage causes increased tone and hyperreflexia. The most common site of damage in these cases is the internal capsule (which contains the corticospinal tract) and the adjacent putamen, caudate, and globus pallidus.
In spastic paralysis, the muscle tone is increased on the affected side, and reflexes (such as the patellar reflex) are exaggerated. Often there is an abnormal reflex called the **Babinski sign**, in which firm stroking of the sole of the foot causes the big to extend rather than flex.

> *The diagnostic importance of the difference between spastic and flaccid paralysis led to the use of an unfortunate nomenclature by neurologists in the twentieth century; spastic paralysis was called 'upper motor neuron (UMN)' paralysis, and flaccid paralysis was called 'lower motor neuron (LMN)' paralysis. This nomenclature attempted to characterize the corticospinal pathway as the upper motor neuron was a light-hearted way of saying that the pyramidal cells of the motor cortex were similar to the actual motor neurons in the brain stem spinal cord. This terminology is misleading and should be avoided.*

Flaccid paralysis

Damage to the motor neurons or their axons can occur in many different ways. In the cases of motor neuron disease and polio, the cell bodies of the motor neurons are directly affected. Nonetheless, the most common causes of flaccid paralysis are damage to the axons of motor neurons, as occurs in the cranial and spinal nerves, the limb plexuses, and the individual nerves of the limbs. Cranial nerve motor neuron damage can affect the eye muscle nerves (oculomotor, trochlear, abducens), trigeminal, facial, and hypoglossal nerves, and the nerves connected to the ambiguous nucleus (glossopharyngeal, vagus, and cranial accessory). Paralysis caused by damage to cranial nerves will be discussed in detail in another section.

In flaccid paralysis, tone and reflexes are either much diminished or lost. Peripheral paralysis is also accompanied by muscle atrophy. If paralysis is caused by damage to a peripheral nerve, a sensory loss is also present.

Incoordination

Inability to coordinate movements is a classic sign of cerebellar damage. When asked to touch their nose with a finger, the patient's hand may move unaimed and randomly as it gets closer to its target. More subtle forms of incoordination may be a sign of parietal lobe damage.

Abnormal spontaneous movements

Tremor

Tremor is a rhythmic oscillation with the alternating activity of muscular agonists and antagonists, resulting in shaking of the affected body part. A tremor in the hands is a well-known sign of Parkinsonism. However, it may also occur in multiple sclerosis, cerebellar damage, stroke, and traumatic brain injury. It can also occur in individuals with no underlying neurological disease.
The two most important forms of tremor are resting tremor and action tremor. In a resting tremor, the tremor disappears as soon as the corresponding muscles perform a voluntary movement. Conversely, action tremor increases with the movement's strength and is not present at rest.

Tics

Tics are involuntary, rapid, repetitive muscle spasms that characteristically occur in Huntington's disease or Tourette's syndrome.

Choreoathetoid movements

Choreoathetoid movements are slow writhing (twisting) movements of the limbs and trunk that are characteristically seen in severe cases of cerebral palsy or Chorea Huntington.

Sensory loss

This section will focus on sensory loss associated with the skin, including loss of the senses of touch, deep pressure, pain, and temperature. Sensory loss due to damage to individual cortical sensory areas or the sensory cranial nerves supplying olfaction, vision, taste, hearing, and balance will be dealt with separately.
The most common cause of cutaneous sensory loss is peripheral neuritis – progressive damage to peripheral nerves of the limbs that occurs in diseases such as diabetes. Damage to individual spinal nerves or individual limb nerves (such as the radial or median nerves) is associated with specific areas of sensory loss that can lead to a diagnosis. At this introductory level of study, it will be sufficient to focus your attention on the following:

- damage to the C4, C6, T1, L4, and L5 spinal nerves
- damage to the axillary, radial, ulnar, median, and sciatic nerves

Damage to spinal nerves and limb nerves affects all types of cutaneous sensation. Nevertheless, central damage to sensory pathways in the spinal cord is restricted to certain sensations. Damage to the dorsal column system affects touch and deep pressure sensations. In contrast, damage to the spinothalamic tracts affects the sensations of pain and temperature (lateral spinothalamic tract) or touch (anterior spinothalamic tract).

Cognitive and neuropsychological Symptoms

Aphasia

Aphasias are acquired speech disorders. Damage to speech areas in the dominant cerebral hemisphere can result in a loss of ability to understand speech (receptive aphasia or sensory aphasia) or a loss of ability to communicate by speech (expressive aphasia or motor aphasia). The left hemisphere is dominant in nearly every right-handed and in most left-handed people. Common causes of damage in the speech areas are arterial blockage, traumatic brain injury, or tumors.

The sensory speech area is located on the posterior third of the upper surface of the superior temporal gyrus, posterior to the primary auditory cortex. The upper surface of the superior temporal gyrus is called the planum temporale. In right-handed people, the surface area of the planum temporale is much larger on the left side than on the right – consistent with the large area occupied by the sensory speech area. The sensory speech area is named after Carl Wernicke, a German neurologist of the late nineteenth century. It is defined as area 22 in the Brodmann classification of cortical areas.

The motor speech area is located in the inferior frontal gyrus of the dominant cerebral hemisphere. Motor or expressive aphasia) is named after the French physician and anthropologist Paul Broca, who lived in the middle of the nineteenth century. The inferior frontal gyrus comprises three parts – opercular, triangular, and orbital (from posterior to anterior). The parts most closely associated with Broca's aphasia are the triangular part (Brodmann's area 45) and the opercular part (area 44).

Apraxia

Apraxias are disorders of motor planning characterized by an inability to carry out skilled movements and gestures on demand in the absence of sensory loss or paralysis.
Apraxia can be caused by trauma, stroke, or tumor. Apraxia is traditionally considered a sign of parietal lobe damage, but it can also result from damage to the prefrontal cortex or the corpus callosum.
It can present in several ways, the most common of which are orofacial apraxia and constructional apraxia. Orofacial apraxia is the inability to carry out facial movements on demand, such as licking one's lips, winking, or whistling, even though no paralysis is present. Constructional apraxia is the inability to draw, construct, or copy simple patterns. These patients have difficulty copying a simple diagram or drawing basic shapes.

Memory loss

Short-term memory impairment refers to a reduced or suspended ability to remember information just received; long-term memory loss is an inability to recall learned information or experiences from the past.
The brain area that initially registers episodic memories is called the hippocampus, a distinctive area of the three-layered cortex in the temporal lobe of the human brain. The hippocampus occupies more than 10% of the cerebral cortical volume in many small mammals. However, in humans, the hippocampus's size appears small compared to the massive overgrowth of the frontal and temporal lobes. The cortical folding in the mammalian hippocampal region is striking. It is easy to recognize the major subdivisions in histological sections: the dentate gyrus, the CA regions, the subiculum, and the entorhinal cortex.
The hippocampus is crucial for memory formation, but it is believed that long-term memories are stored over a much wider area of the cortex. The ability of the cortex to remember underlies our knowledge and understanding of the world, allowing patterns to be recognized and details to be filled in when they are missing. In this way, most cortex connections are created based on experience.

Semantic and episodic memory

The ability of the human cortex to store thousands of memories allows us to make fine distinctions and accumulate detailed knowledge of the way the world works. This enables us to make accurate and useful predictions about the results of planned behaviors. The recollection of experience can be classified as either semantic or episodic. Semantic memory relates to a generalized impression of several experiences, such as the movement of falling objects, the texture of water, and the meaning of a pattern of sounds. Semantic memory enables understanding rather than a recollection of specific experiences.

On the other hand, episodic memory is linked to specific experiences at a particular time and place. The distinction between the two forms of memory is not always clear-cut. For instance, we may know something to be true (semantic memory). Nevertheless, we may recall a particular learning experience that taught us that fact (episodic memory). Many pieces of knowledge depend on many episodic experiences. However, the semantic memory can remain in the long term even when the individual episodes are forgotten.

The case of Henry Molaison

The hippocampus is primarily involved with the formation of memories, and it does not appear to be directly involved in consciousness. However, without the hippocampus, an individual may experience severe distortions of consciousness because, without access to recent memories, they cannot create a context for their surroundings. This is supported by studies of many patients with hippocampal damage, including the famous case of Henry Molaison (HM), a patient of William Scoville whom Brenda Milner has intensively studied. Henry Molaison underwent a bilateral removal of the medial components of the temporal lobes, including the hippocampus, in an attempt to treat non-responsive, severe epilepsy. After the surgery, he reported that his conscious state was abnormal. He felt he was "constantly waking up from a dream" with "everything looking unfamiliar" and could not form new memories of his experiences after the surgery. He was stunned and distressed by the aging of his face in the following decades, leading to the removal of the mirrors from his accommodation.

Other neurological signs

Epileptic attacks

Epileptic attacks are caused by storms of electrical hyperactivity in the brain. The most striking form of epilepsy is a generalized seizure: The person becomes unconscious and suffers violent tonic-clonic muscle spasms. This type of seizure was traditionally called *grand mal* epilepsy. In other forms of epilepsy, the episode appears as an 'absence,' a short period during which the person appears to have lost touch with their surroundings and stares blankly ahead. These absence seizures were formerly called *petit mal* seizures.

Epileptic attacks can be triggered by various things besides the "classical disease epilepsy." Important triggers are drugs and medication, fever, tumors, electrolyte disorders, hypoglycemia (also due to insulin overdose), sleep deprivation, or extreme stress situations.

Sleep disorders

Sleep is essential for all vertebrates. While we often think of sleep as a way to rebuild energy, the body, and the brain continue to use energy while we are asleep. Very deep sleep may be a

way to conserve resources when intelligent behavior is not required, such as hibernating over the winter of some animals.
In humans, sleep runs in 90-minute cycles. In each iteration, the proportion of slow-wave activity in the electroencephalograph gradually becomes greater, eventually reaching widespread slow-wave activity characteristic of deep sleep. The end of one cycle is followed by short periods in which brain activity resembles an awake state, called rapid eye movement (REM) sleep. Subjects who were woken from various stages of sleep reported most often that dreams occur during REM periods. On the other hand, the mental states of deep sleep are vague and not dream-like. In addition to marked changes in the brain's electrical activity, the activity of various neurotransmitter systems changes from deep sleep to REM sleep. REM sleep is characterized by high levels of cortical acetylcholine (ACh), reflecting a high level of activity and arousal. During slow-wave sleep, ACh levels are much lower, and activation of the hippocampal in this state is associated with the consolidation of experience into long-term memory.

Sleep regulation

The regulation of sleep depends on the function of a small number of specific cell groups in the hindbrain, hypothalamus, and preoptic area. Certain areas in the brain stem and hypothalamus have widespread projections to the cerebral cortex responsible for keeping us awake and alert. These 'awake' centers are the locus coeruleus, the serotonin raphe system, the dorsal tegmental nuclei, and the tuberomammillary nucleus of the hypothalamus. An unusual feature of these nuclei is that each one relies on a specific transmitter substance not found in the other members of this group. In the case of the locus coeruleus, this is noradrenaline; in the raphe, it is serotonin; in the tegmental nuclei, it is acetylcholine; and in the tuberomammillary nucleus, it is histamine. Sleep occurs when activity in these centers is shut down.

In the 1990s, the Saper group at Harvard began an ambitious project to unravel the pathways that create sleep and awake states. By tracing the input connections of the known awake centers, they discovered that a master sleep switch lies rostral to the hypothalamus in the preoptic area. The sleep switch is a small cell group called the ventrolateral preoptic nucleus (VLPO). The VLPO makes inhibitory connections with all the 'awake' centers (locus coeruleus, raphe nuclei, the cholinergic tegmental nuclei, and the histamine nucleus of the hypothalamus). When the VLPO is activated, it switches off the awake centers, and the cerebral cortex goes to sleep. Damage to the VLPO can produce pathological insomnia, a permanent inability to sleep. The activity of VLPO is principally controlled by input from the visual pathway - fibers in the optic nerve connect to the suprachiasmatic nucleus, which is the 24-hour clock in the brain. This nucleus tells the VLPO when it is dark, and therefore a good time to go to sleep, and when it is light and time to wake up.

A critical component of the sleep circuitry is the loop that stabilizes the system. If the brain had only reciprocally interconnected centers for sleep and alertness, there might be a tendency for behavior to flip unpredictably between sleeping and waking, as happens in narcolepsy. To prevent this, the dorsomedial nucleus of the hypothalamus has a stabilizing role, continually monitoring activity and behavior and recognizing when danger or other factors make sleep inappropriate, even when VLPO has calculated it is time to sleep.

Sleep disorders are widespread and affect about 10% of the general population.
In most cases, these are due to external factors, poor sleep hygiene, physical or mental illnesses, or medication use. Other causes are found in a smaller proportion and are often related to a disruption of the regulatory networks mentioned above.

Neurological Tests

Neurological tests are used to supplement information gathered from the history and physical examination.
Each technique has its own advantages and disadvantages, so it is vital to use the proper method for the suspected disease.

Liquor diagnostics *(examining the cerebrospinal fluid) provides important information about possible inflammatory processes in the central nervous system. It can also detect some hemorrhages or tumors but is used less frequently.*

Neuroimaging *can non-invasively image the structures of the skull and brain. Each technique in this category is particularly good at imaging certain structures or processes. Magnetic resonance imaging (MRI) is best suited for imaging soft tissues, such as the brain. Computer tomography (CT) is ideal for acutely examining the skull's bone structure, such as a suspected skull fracture. For a quick and reliable diagnosis of strokes, contrast media (substances that show up extremely well in imaging) can be additionally administered.*

While neuroimaging can visualize many anatomical structures, it is limited in its ability to visualize the activity or the function of neurons. This is an excellent strength of ***neurophysiological examination methods****. Electroencephalography (EEG) can show cerebral dysfunctions and has a central role in epilepsy diagnostics. The measurement of nerve conduction velocity is essential for examining peripheral nerves, and electromyography (EMG) is used to differentiate between neuronal and muscular damage.*

Biopsies*, i.e., the explicit removal of tissue, are sometimes necessary to diagnose or stage certain diseases precisely. They are mainly used to diagnose tumors or peripheral nerve and muscle diseases.*

Examining cerebrospinal fluid

Cerebrospinal fluid (CSF) can be obtained by lumbar puncture (spinal tap). A long needle is used to reach the CSF in the subarachnoid space in the vertebral canal between the fourth and fifth lumbar vertebrae. Because the spinal cord extends no lower than the second lumbar vertebra, there is no risk of damage to the spinal cord in this procedure. Examination of CSF is essential in cases of suspected bacterial meningitis where pus can be found in the CSF or subarachnoid hemorrhage finding blood in the CSF.

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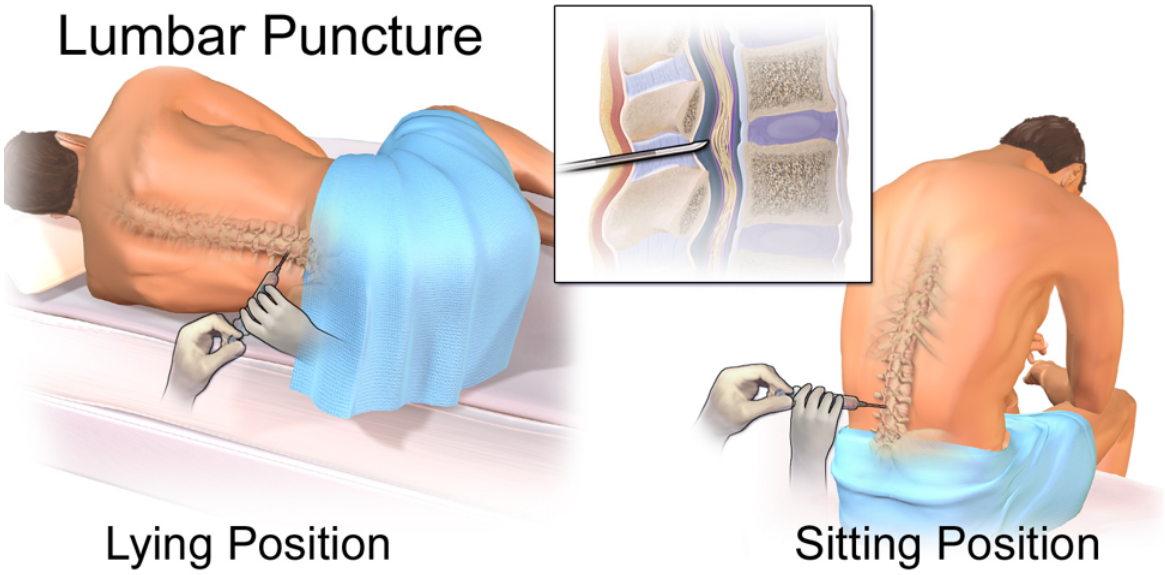
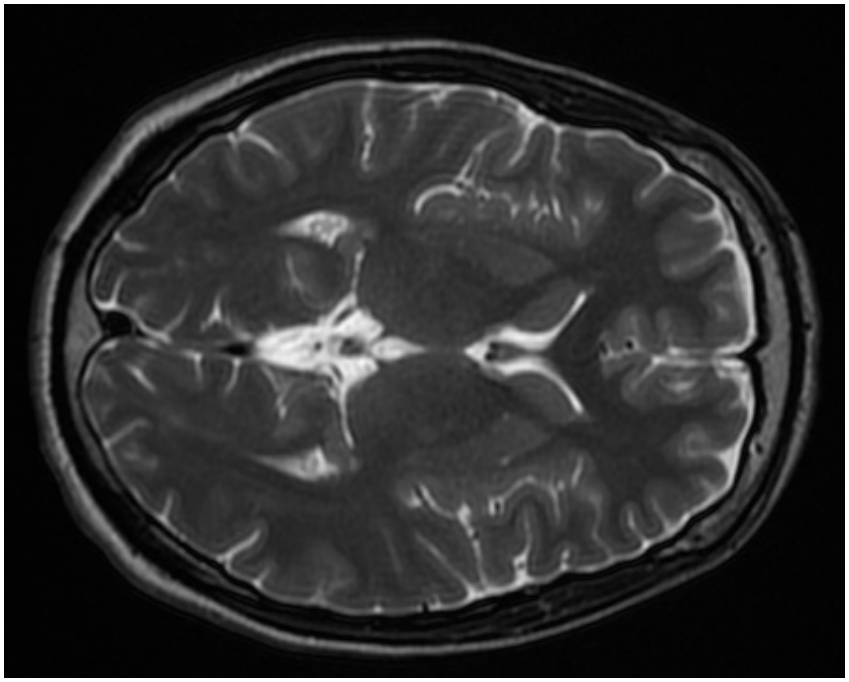


Different ways to perform a lumbar puncture.
Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436., CC BY 3.0, via Wikimedia Commons

Imaging

Magnetic Resonance Imaging (MRI)

MRI can produce detailed images of brain tissues without using harmful radiation. It can differentiate major neuroanatomical structures (cortex, white matter, nuclei) and can reveal the presence of a variety of pathological processes, such as tumors, inflammation, ischemia, and degeneration with high sensitivity. MRI is widely used in hospitals and clinics for medical diagnosis, disease staging, and follow-up after treatment. Compared with CT scans, MRI scans typically take longer, are noisy, and require the subject to lie in a narrow, confining tube.



***Axial MRI of a human brain, with no pathology visible**. Novaksean, CC BY-SA 4.0 via Wikimedia Commons*

CT scans

X-rays penetrate the head during a CT scan, and the absorption of radiation by different tissues can be measured. Because different tissues have different densities, they absorb radiation in different ways. In the CT scan, two radiation sources located at opposite sides of a circular x-ray detector are rotated around the head of the patient. These data are then integrated to produce a 3D digital reconstruction of the skull and brain.

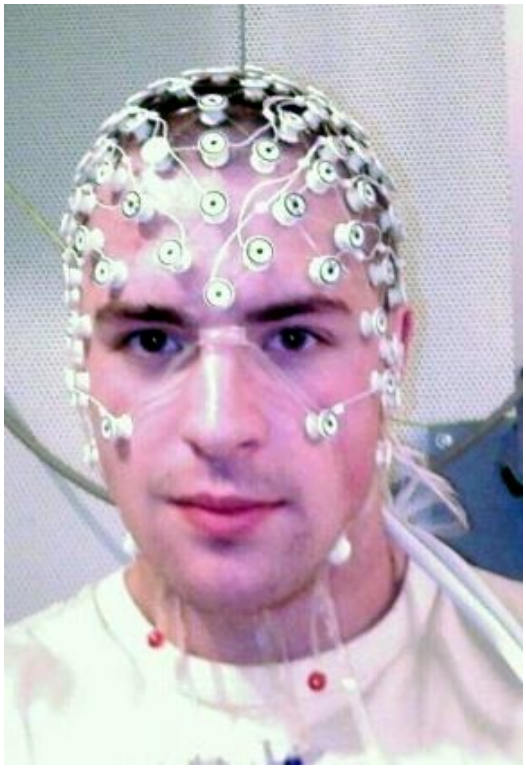
The CT scan was one of the first neuroimaging techniques to be used in patients and is still widely used because it is cheap and fast. However, it has some significant disadvantages. X-rays can be harmful. However, it is still commonly used because it is comparatively cheap and fast. Furthermore, CT scans show the anatomy of the cranial bones in excellent detail, so CT is often used in emergency room cases to check for fractures.

Neurophysiological examination methods

Electroencephalography

The electroencephalogram (EEG) records the electrical activity of the brain using surface electrodes placed on the scalp. The EEG is important in the diagnosis of epilepsy. The EEG can detect different electrical waveforms which reflect the state of alertness of the subject. These include:

- alpha-waves indicate a relaxed state of awareness
- beta-waves appear during concentration and focused attention
- theta-waves indicate fatigue and the onset of sleep
- delta waves appear during deep sleep.



An EEG recording setup.

The EEG pattern does not mature until the teenage years, and the EEG in infants often shows very slow and irregular waves.

Nerve conduction studies (NCS)

Nerve conduction studies are used to detect abnormalities in electrical conduction in peripheral nerves. These studies are used to monitor the progress of demyelinating disorders of the peripheral nerves.

Electromyography

Electromyography measures muscle action potentials to assess whether the underlying problem is related to nerve supply or intrinsic muscle disease. They can be used to assess the level of muscle atrophy resulting from a peripheral nerve lesion. In this way, the impact of nerve injury can be assessed over time.

Biopsy

Biopsy involves the surgical removal of tissue for microscopic examination.
A biopsy can provide information that could not be obtained through other methods. However, a large brain biopsy will remove a functioning piece of the brain, which may have long term consequences.

Neurological Disorders

Inflammatory processes in the central nervous system

Meningitis and encephalitis

Bacterial and viral infections can cause meningitis (if the meninges are affected) or encephalitis (if the brain is directly infected). The two conditions can occur in combination, which is called meningoencephalitis.
The characteristic symptoms of meningitis are headache and neck stiffness in the presence of fever. The most important diagnostic test is a lumbar puncture, which can reveal an elevated white cell count and the presence of protein in the cerebrospinal fluid. Bacterial or viral infections usually trigger the diseases, less frequently by fungal, parasitic, or other infections. Bacterial meningitis can be effectively treated with antibiotics. Bacterial meningitis caused by *Haemophilus influenzae type B* (HIB), *Pneumococcus*, and some forms of *Meningococcus* can be prevented with childhood immunization.
Viral encephalitis can have serious long-term consequences such as deafness, epilepsy, hydrocephalus, and cognitive deficits.

Poliomyelitis

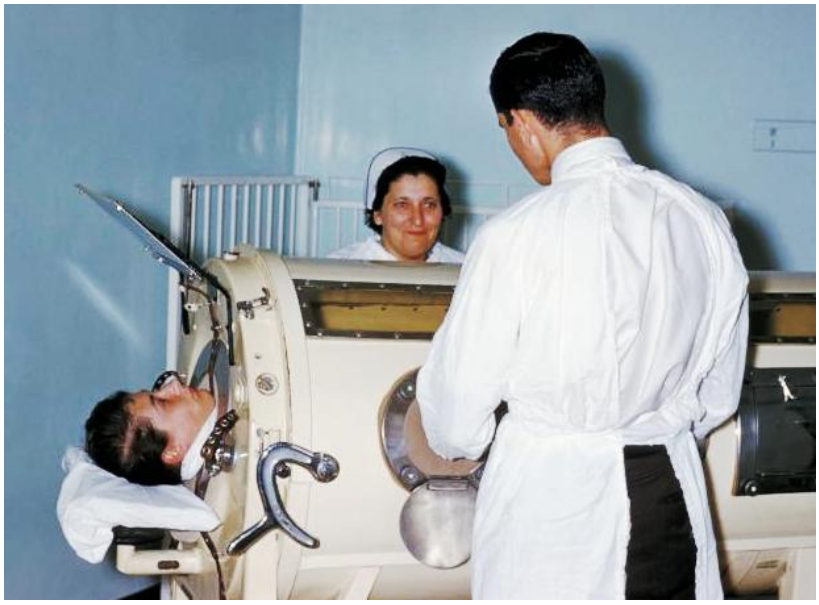
Poliomyelitis is a paralytic disease caused by the poliovirus. Since the introduction of vaccination programs, it has been eradicated nearly everywhere in the world. Nevertheless, the disease illustrates some intriguing facts about neuroscience.

World map representing the incidence of poliomyelitis (wild virus) according to the WHO 2015, orange: 21 to 30 confirmed cases, yellow: 1 to 10 confirmed cases, grey: No wild virus; *Pazuzupa, CC BY-SA 3.0, via Wikimedia Commons.*

In most cases, the poliomyelitis infection occurs without any symptoms at all. Symptomatic cases are most often accompanied by vomiting and diarrhea. Only about 1-2% of the cases involve the central nervous system, which can lead to paralysis.
The poliovirus uses the neurotransmitter reuptake mechanism to enter the central nervous system via the nerve-muscle synapse. The virus then travels retrogradely along the motor neuron axons to reach the motor neuron cell bodies in the spinal cord or hindbrain. Once the poliovirus reaches the motor neuron cell body, it causes fatal damage, which results in paralysis. Unfortunately, the damage is permanent because the motor neurons cannot regenerate. Damage to mo-

tor neurons in the spinal cord below the mid-cervical region results in paralysis of one or more limbs. The affection of motor neurons in the hindbrain and/or the upper cervical region lead to a paralysis of the swallowing and breathing muscles. This is fatal unless a mechanical respirator is used to support the breathing.

> *During the epidemics of the 1950s, hundreds of thousands of people worldwide were paralyzed by polio infections every year. Back then, the respirators were massive metal containers called iron lungs.*



Hospital staff is examining a patient in a tank respirator, iron lung, during the Rhode Island polio epidemic. The iron lung encased the thoracic cavity externally in an air-tight chamber. The chamber was used to create negative pressure around the thoracic cavity, thereby causing air to rush into the lungs to equalize intrapulmonary pressure; *This media comes from the Centers for Disease Control and Prevention's Public Health Image Library (PHIL), id: 2624.*

Prion Diseases

Creutzfeld-Jacob disease (CJD)

CJD is caused by so-called *prions* (for **pr**oteinaceous **i**nfecti**o**us age**n**ts) – the presence of an abnormal variant of the normal prion protein. Prions are misfolded proteins with an increased β-sheet structure. They can force healthy proteins into a conformational change. The normal prion protein (PrPc) is physiologically a membrane-tethered protein, mainly expressed in lymphocytes and neurons. The misfolded proteins (PrPsc) cannot be degraded by the body and accumulate into plaques. These aggregates disrupt the neuronal functions and cause rapidly progressive dementia, which leads to death usually within one year from the onset of the disease. The prion CJD occurs spontaneously in one in every million people worldwide.
In addition to clinical symptoms, MRI images and cerebrospinal fluid diagnostics can provide clues. A definitive diagnosis of CJD is only possible post-mortem by histopathological and immunohistochemical methods. There is currently no treatment available.

Variant Creutzfeld-Jacob disease (vCJD)

Variant CJD in humans was caused by the transfer of a prion disease from animals to humans in the UK in the early 1980s. Scrapie is a prion disease in sheep which was transmitted to cattle.

It is most likely that scrapie was transmitted to cattle by adding sheep abattoir by-products to cattle stock feed supplements given to cows. The result was an epidemic of bovine spongiform encephalopathy (BSE) in cattle in the UK. BSE is the bovine equivalent of scrapie and was named mad cow disease. It was first thought that BSE could not be transmitted to humans eating meat from afflicted cattle. However, this belief was tragically wrong, and many people were infected in the UK. The human disease induced by the BSE prion is described as variant CJD (vCJD). Beef products were withdrawn from sale in the UK, and thousands of infected animals were slaughtered and burned. Despite eradicating the disease from farmed cattle, new human cases of vCJD continue to appear in the UK. This is because prion diseases can have very long incubation periods, up to 30 years or more.

Rabies

Rabies is caused by an eponymous virus present in the saliva of infected bats and dogs and can be transmitted by bites or scratches from these animals. The virus enters neuromuscular synapses (like poliovirus) and then uses retrograde axonal transport to get to the motor neuron cell bodies in the spinal cord. The remarkable feature of the rabies virus is that it can cross synapses to reach all the neurons that connect with the infected neuron. In this way, the virus can slowly spread to virtually all the cells in the spinal cord and brain. Eventually, sometimes years after the initial infection, the cells degenerate, and death inevitably follows. This terrible process can be interrupted if a particular vaccination is administered within a few days of transmission from a bite or scratch from a rabid animal.

In untreated cases, the first symptoms are usually headaches, depressive moods, fever, and exhaustion. Later, this escalates into confusion, hallucinations, aggressive behavior, and muscle spasms. The disease is almost always fatal within seven to ten days after the onset of neurological symptoms. Diagnosis is made based on a history of an animal and, if necessary, neck skin biopsy.

Neuroscience research uses the ability of the rabies virus to cross synapses for nerve tracing techniques. Neural circuits can be retrogradely mapped using a pseudorabies virus, a non-dangerous relative of the original rabies virus.

Multiple sclerosis (MS)

Multiple sclerosis is a central nervous system disease with inflammatory (autoimmune) and neurodegenerative components. The disease causes focal central nervous system lesions characterized by demyelination of nerve fibers and axonal damage. MS is a relatively common cause of neurological disability, especially in young adults, affecting women up to three times more than men. The cause of the disease is currently unknown. However, recent studies provide strong evidence that MS may be related to a previous infection with Epstein-Barr virus.

> *MS is associated with dysregulation of the patient's immune. This leads to a mistaken activation of T lymphocytes which then attack oligodendrocytes and the production of antibodies against myelin by recruited B cells. Both mechanisms destroy the myelin sheaths within the white matter (demyelination), ultimately causing neuronal cell death.*
> *Since MS is a disease that usually progresses in relapses, the affected brain areas can partially regenerate and rebuild the myelin sheaths (remyelination) but not the neurons between two attacks. Insufficient regeneration leads to the formation of astrocyte scars around the axons. These lesions are called plagues and are the characteristic signs of MS, eventually leading to the name of MS since the Greek word for "plaque" is skleros.*

The symptoms of multiple sclerosis characteristically follow a relapsing pattern, in which episodes of damage are separated by months without new symptoms. Over time the episodes of damage become more frequent, and there is an overall gradual decline in the person's health. Symptoms vary from person to person, depending on the location of the lesions. However, a common first episode involves damage to one optic nerve resulting in blurred vision or blindness. Later symptoms may include fatigue, muscle weakness, lack of coordination, sensory abnormalities, intention tremor, and paralysis.

> *When axons become demyelinated, saltatory conduction is no longer possible. Consequently, action potentials must be generated more frequently, and excitations can spread unspecifically in the tissue. The former results in a significantly increased energy demand, explaining the general fatigue of many patients. The unspecific excitations combined with the sheathed nerve cells' destruction can lead to general coordination and perception disorders.*

The diagnosis is made on the basis of clinical symptoms and the detection of plague lesions with MRI. Antibodies against myelin, so-called oligoclonal bands, can be seen in CSF obtained by lumbar puncture.
In recent years, effective symptomatic drug treatments for MS have been introduced.

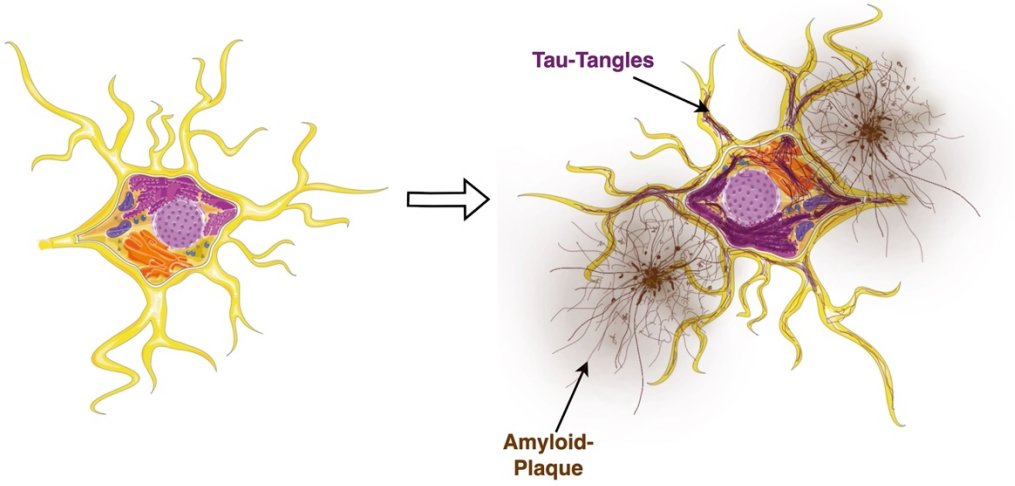
Neurodegenerative Diseases

Dementia and Alzheimer's disease

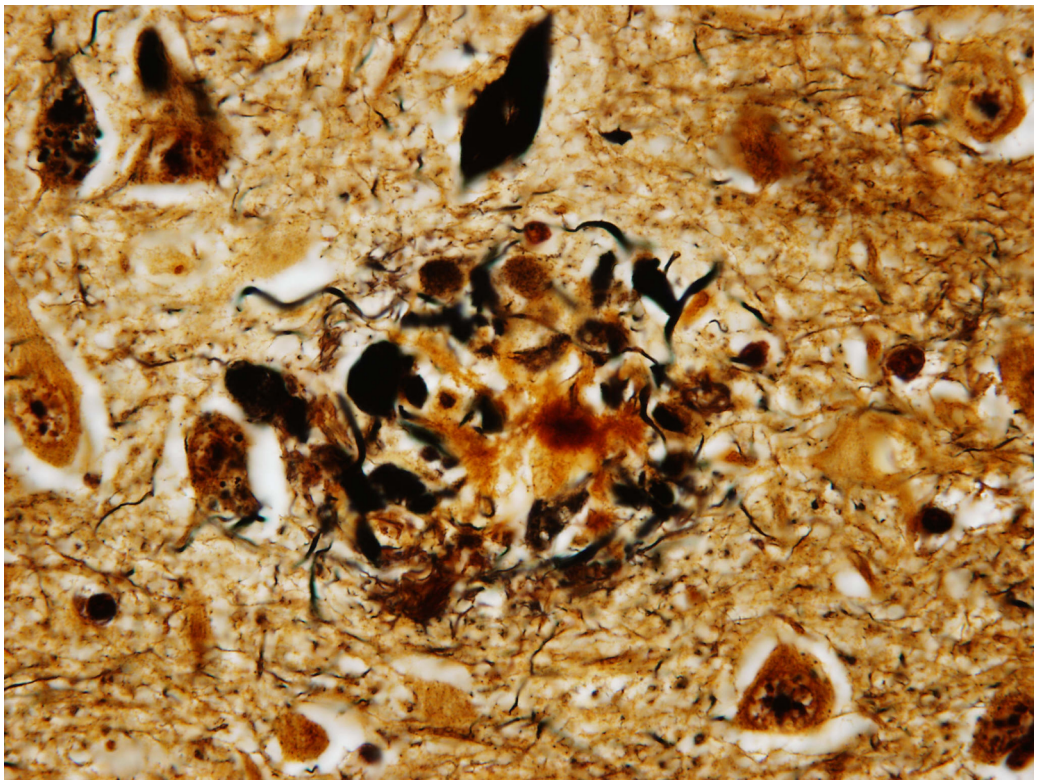
Dementia is characterized by an acquired, progressive impairment of brain function. It is due to progressive brain atrophy, disproportionately greater than age-related physiological cerebral loss.
Individuals with dementia suffer progressive impairment in memory, thinking, and planning, making it difficult to carry out everyday activities. There may also be emotional problems, speech problems, and lack of motivation. The most common early symptom of dementia is short-term memory loss, such as the inability to recall a particular word.
The most common cause of dementia is Alzheimer's disease, accounting for about 65% of cases. The second most common cause is chronic vascular disease.

Alzheimer's disease (AD)

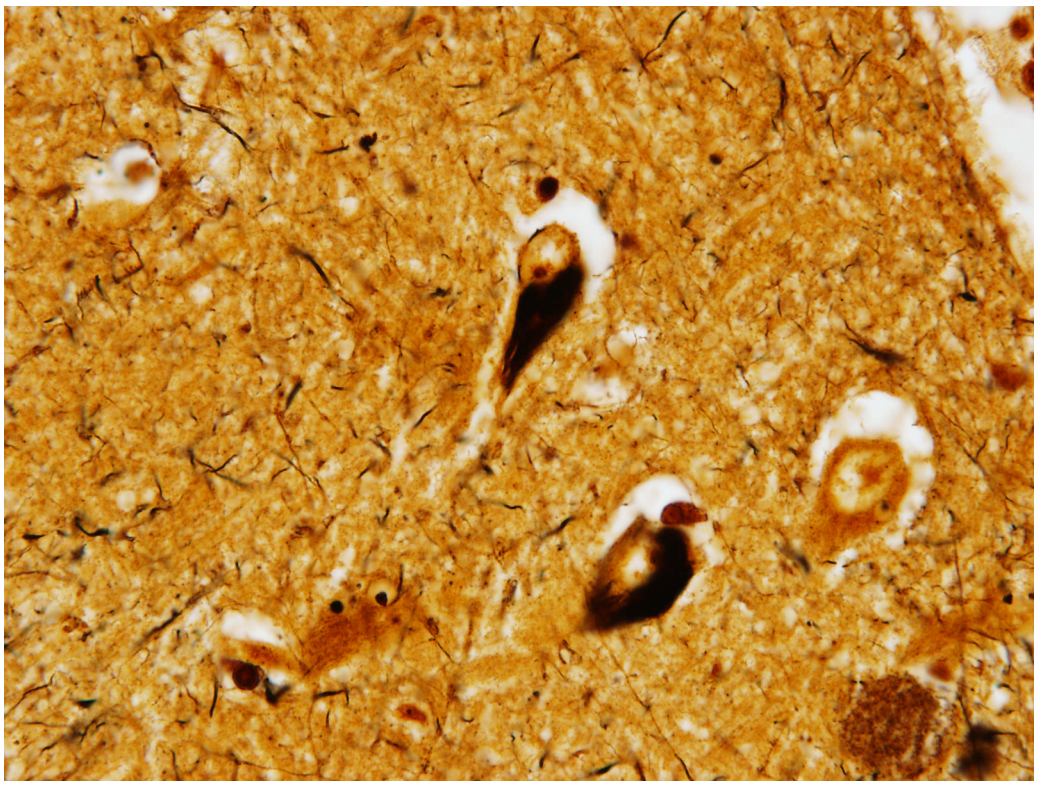
Alzheimer's disease is the most frequent cause of dementia worldwide. It is associated with a progressive and relentless loss of nerve cells in the forebrain. While AD is much more common in older individuals, dementia is not a normal aging process. The earliest symptoms may be minor episodes of memory loss. However, as the disease advances, the cognitive decline becomes overwhelming, eventually making it impossible for the patients to take care of themselves.
The part of the brain first affected by Alzheimer's disease is the hippocampus, followed by temporal and parietal lobe atrophy.
Histologically AD is characterized by the aggregation of specific proteins. Due to a defective AP-protein (APP) degradation, amyloid-beta plaques accumulate extracellularly. Additionally, hyperphosphorylated tau proteins accumulate intracellularly to form so-called neurofibrillary tangles.
Both of these protein deposits lead to a disturbance of normal cell functions, resulting in cell death.
Patients commonly die of infections such as pneumonia within four years after AD diagnosis.



Schematic visualization of the main histopathological features of Alzheimer's Disease.



Amyloid-beta aggregations, Bielschowsky silver impregnation; *Image courtesy of Prof. Christine Stadelmann, University Medical Center Göttingen.*



Hyperphosphorylated tau proteins accumulate intracellularly to form neurofibrillary tangles, Bielschowsky silver impregnation; *Image courtesy of Prof. Christine Stadelmann, University Medical Center Göttingen.*

Alzheimer's disease is usually diagnosed using neuropsychological tests like the mini-mental state examination or other test batteries. A loss of cortical brain tissue can be observed in CT and MRI images. Examination of CSF from lumbar puncture may reveal an increase in phospho-tau (released by cell death) and a decrease in amyloid-beta (due to aggregation) content.
Despite intensive research on the underlying causation of AD, therapeutical options are minimal. Acetylcholinesterase inhibitors are often prescribed to improve symptoms related to the degeneration of cholinergic neurons. This helps that even small amounts of neurotransmitters can still have an effect.

Parkinsonism syndromes

Parkinsonism refers to a group of motor system diseases in which the cardinal symptoms are tremor, rigor, akinesia, and postural instability due to a lack of dopamine.

Front and side views of a man portrayed to be suffering from Parkinson's disease; *William Richard Gowers (1886).*

Parkinson's disease (PD)

Parkinson's disease (PD) is a motor system disease that mainly occurs in older adults, affecting about 1% of individuals older than 60. Although the underlying cause of PD is unknown in the majority of cases, the disease features a loss of the dopaminergic neurons in the substantia nigra. The substantia nigra sends dopaminergic axons to the forebrain, mainly to the striatum (caudate and putamen). In PD, most of the dopamine cells of the substantia nigra die, disrupting its normal role in posture and movement. The main symptoms are tremor in the hands, a shuffling walk, and muscular rigidity, making it difficult for the person to initiate a movement. There is no paralysis, but the rigidity in many muscles makes it hard to carry out any voluntary movement except very slowly. Because of this, the patient may appear to be emotionless and apathetic.
Some cases of PD are accompanied by cortical degeneration, which may lead to dementia.
For many years, the main treatment of PD has been the administration of a dopamine precursor to increase the production of dopamine in the remaining substantia nigra neurons. The chemical precursor to dopamine is called L-dihydroxyphenylalanine (L-DOPA). This treatment can reduce the severity of symptoms in many cases, but it becomes less effective after some years because too many neurons have died to make effective use of the L-DOPA.

To counteract these effects, L-DOPA can be used in combination with inhibitors of dopamine-degrading enzymes and dopamine agonists.

> *In drug-resistant or younger patients, deep brain stimulation has been used to control symptoms. In deep brain stimulation, electrodes are implanted to stimulate certain brain areas continuously. Up until about 2005, the main target for electrode placement was the subthalamic nucleus which lies between the thalamus and hypothalamus, but more recently, the adjacent zona incerta has emerged as a much more suitable target.*

Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is also called motor neuron disease. It is a rapidly progressive neurodegenerative disease, first affecting mainly the motor neurons of the spinal cord and brain stem but which may later affect the motor cortex and other cortical areas. Most patients usually die within three years of diagnosis because of a paralysis of the respiratory and swallowing muscles.
The disease commonly begins in middle age, and men are affected more often than women. The underlying cause is unknown, but there is a genetic link in 5-10% of the cases.
There is no curative therapy, but numerous symptomatic treatment options can prolong survival and improve quality of life.

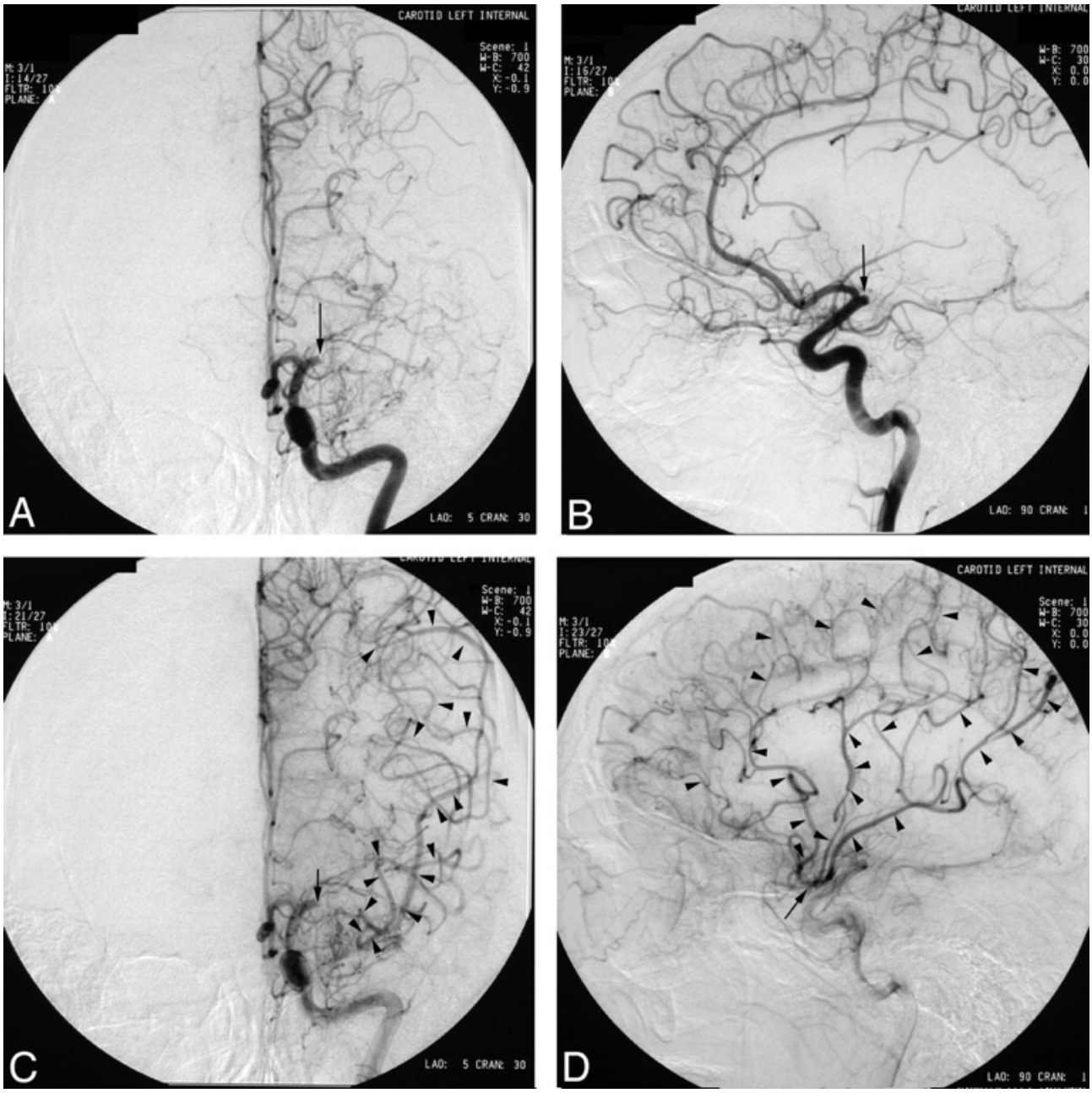
Stroke

A stroke is an acute disturbance of the brain's blood supply or parts of it. Due to this interruption, the neurons can no longer be supplied with oxygen and glucose and die as a result.

> *The term 'stroke' refers to an event in which a person is suddenly struck down by something that happens in their brain.*

The occlusion of a blood vessel usually causes a stroke (*ischemic stroke*). Nevertheless, rupture of blood vessels is also a possible cause (*hemorrhage*). The main risk factors for stroke are high blood pressure, diabetes mellitus, heart conditions, smoking, and being male.
Depending on which artery (and therefore which brain region) is affected, a stroke might result in paralysis, loss of touch sensation, loss of the ability to speak, or all of these. Characteristic is the sudden onset of symptoms. Because each cerebral hemisphere controls muscles on and receives input from the opposite side of the body, the symptoms usually affect the opposite body side as the stroke. The inability to speak (aphasia) is often seen when the speech-dominant hemisphere (usually the left) is affected. In some cases of stroke, the damage may be very localized (such as paralysis of the leg muscles alone). In more severe cases, like massive arterial bleeding, the damage may involve most of one cerebral hemisphere. In these critical cases, the brain swelling may press the hindbrain respiratory centers against the skull, resulting in loss of breathing and death.
One area of the cerebral hemisphere that is particularly sensitive to arterial damage is the internal capsule. The internal capsule is the great fiber sheet that connects the cerebral cortex with the rest of the brain and spinal cord. Even relatively minor damage to this bundle can be catastrophic, in the same way as cutting a central telephone cable can affect a whole suburb.
The most important diagnostic step is to quickly distinguish between a stroke due to artery blockage or bleeding. CT is usually used for this since it is fast. In the case of an ischaemic stroke, reopening the blockage can be done by anticoagulants or mechanically.

> *To save as many neurons as possible, the reopening of the arteries must happen as quickly as possible. This is why the following saying circulates among neurologists and emergency physicians: "**Time is brain!**"*



Anteroposterior (A and C) and lateral (B and C) images from a left internal carotid artery angiogram obtained during the early (A and B) and delayed angiographic phases (C and D) in a patient with acute ischemic stroke due to occlusion at the middle cerebral artery (arrow); *Gregory A. Christoforidis et al. AJNR Am J Neuroradiol 2005:26:1789-1797.*

Epilepsy

Epilepsy is a chronic brain disorder characterized by repeated epileptic seizures - convulsions or fits. Physiologically, the cerebral cortex maintains a close balance between excitation and inhibition. When this balance fails, it can result in hyperexcitation, causing epilepsy. One overreactive region can stimulate others and cause storms of electrical activity to spread over the whole cerebral cortex. Since the regulatory mechanisms for balancing excitation and inhibition are complex, the causes of epilepsy are challenging to discern in many cases. In some cases, an evident focal cause, such as a tumor or injury, can be detected and treated with surgery. However, in most cases, people with epilepsy are treated with a combination of drugs that alter the actions of excitatory or inhibitory neurotransmitters.
Unfortunately, these medications affect the entire cortex, so side effects are very common and usually very frustrating. Often a long search has to be done to find a treatment balancing the maximum benefits with minimal side effects.
The most important diagnostic tool for epilepsy is the EEG. The most striking form of epilepsy is a generalized seizure. The person becomes unconscious and suffers violent tonic-clonic muscle spasms. This type of seizure was traditionally called 'grand mal epilepsy.

> *Temporal lobe epilepsy (TLE) is a particular form of epilepsy characterized by abnormal behavior. TLE can be triggered by scarring from damage to the medial side of the temporal lobe. These injuries can occur during a difficult birth when pressure on the cerebrum pushes the tip of the temporal lobe against a ridge of dura mater and causes loss of blood supply and damage. Later in life, these areas of scar tissue may trigger electrical disturbances, which spread through the temporal lobe. Because aggressive behavior is sometimes a symptom of TLE attacks, many of the sufferers were sent to prison or psychiatric hospitals in the past. During the 1960s, it was recognized that this syndrome was simply a form of epilepsy, which can be successfully treated with antiepileptic drugs. TLE mainly affects structures on the medial side of the temporal lobe, including the hippocampus, uncus, and the amygdala. The study of patients with TLE may give us clues about the functions of these complex areas within the temporal lobe. For example, patients frequently experience abnormal smell sensations when having a temporal lobe seizure, which we can reasonably attribute to the uncus. The uncus is the site of the primary olfactory cortex. Disturbances of memory function have been attributed to abnormal function of the hippocampus, and aggressive symptoms have been attributed to alteration of function of the amygdala. During the first stage of a TLE seizure, the person may experience an aura of olfactory hallucinations, feelings of déjà vu or jamais vu, feelings of fear or terror, or feelings of depersonalization. As the seizure spreads out to affect a wider temporal lobe area, the person may lose consciousness or may continue to move in a dream-like state. They may perform abnormal repetitive movements such as lip-smacking, chewing, tooth-grinding, or aggressive actions.*

Trauma

Spinal cord damage

Spinal cord damage is most commonly caused by trauma (car accidents or falls). Nonetheless, it can also result from infections, insufficient blood flow, or tumors.
In the acute phase after severe injury, there may be a complete loss of all functions related to the affected area. This is called spinal shock.
Spinal cord injury in the neck region above C5 can cause respiratory paralysis and death. Spinal cord injury at lower cervical levels can result in tetraplegia (paralysis of all limbs). Lesions below T1 can lead to paraplegia, affecting only the lower extremities. Spinal cord injuries commonly result in paralysis of the same and loss of touch sensation and bowel and bladder control of the opposite body side. The vertebral damage can be assessed with an X-ray, CT scan, or MRI. For a comprehensive assessment of the spinal cord, MRI is usually used. An electromyogram can be used to monitor muscle damage and eventually recovery.

Traumatic brain injury (TBI)

Traumatic brain injury is an injury to the skull with consecutive dysfunction and/or structural damage to the brain. It can follow a blow or severe jolt to the head and can result in permanent or temporary damage to the brain. Typical causes are falls, motor vehicle collisions, and violence. Brain trauma is one of the most common causes of death in patients under 40.
During the impact, sudden acceleration and deceleration can smash the brain against the inside of the skull, damaging the areas in contact. The movements can lead to local overstretching and tearing of nerve fibers. Additionally, blood vessels can disrupt, causing bleeding within the brain.
Immediately after trauma, the person may appear confused, may lose consciousness, or may have blurred vision, leading to a diagnosis of concussion. In up to 90% of the cases, such post-traumatic symptoms disappear within the next two weeks. Immobilization is normally not required, but in cases of concern, consciousness and the pupillary reflex should be checked during the first 24 hours. If a headache occurs, it can be treated with pain killers.
In some cases, brain swelling after head injury leads to compression of brain areas that were not damaged in the initial impact. This swelling can happen immediately or anytime up to 5 days after the injury.
CT scans effectively diagnose skull fractures, and MRI can reveal details of cerebral contusion, hemorrhage, and hematoma.

Genetic Conditions

Down syndrome

Trisomy 21, also known as Down syndrome, is the most common chromosomal disorder in newborns (about two-thirds of all cases) and the most common cause of mental retardation in children. In this disorder, parts of or the entire chromosome 21 are present in a third copy.
The disease is associated with characteristic facial features, a delay in cognitive ability, and physical growth. As adults, subjects with trisomy 21 usually have the abilities of an 8-9 year old child. Besides intellectual disabilities, Trisomie 21 carries an increased risk of other disorders like a congenital heart defect or epilepsy.
Because it is almost always caused by mistake during meiosis, it is practically always not inherited. It is possible to identify the disorder prenatally (before birth). A definitive diagnosis follows a chromosome analysis.
There is no cure, but family support, education, and social integration can significantly improve the life quality of those with Down syndrome.

Fragile X syndrome

Fragile X syndrome, sometimes called Martin-Bell syndrome, is the most common monogenetic cause of intellectual disability and the second most common cause of congenital mental retardation after trisomy 21. It is estimated to underlie at least 6% of all with intellectual disabilities.

> *It is a genetic disorder typically due to a higher number of repetitions of a CGG-triplet within the fragile X mental retardation 1 (FMR1) gene (trinucleotide repeat expansion). The insufficient production of the protein FMRP leads to an increased glutamate receptor 5 (mGluR5) synthesis, resulting in impaired synaptic plasticity.*

Besides suffering from intellectual and memory disabilities, the affected children typically have an elongated face and protruding ears. Diagnosis follows the proof of a trinucleotide repeat expansion in the FMR1 gene by human genetic methods, like PCR. Currently, there are no causal therapeutic options.

Rett syndrome

Rett syndrome is one of the most common genetic causes of mental retardation in girls.
It is an X-chromosomal dominant disease that affects females almost exclusively. Males with the condition either die before birth or do not live longer than two years.

> *The Rett syndrome is strongly associated with various mutations in the MECP2 gene found on the X chromosome. The physiological gene product binds to methylated DNA and is involved in regulating thousands of genes. The exact molecular effects depend on the specific mutation but usually include changes in synaptic plasticity, neurotransmitter imbalances, and cortical hyperexcitability.*

The infant is commonly normal at birth but develops symptoms between 6 and 18 months of age. Cognitive skills, especially speaking or walking, begin to stagnate or regress. Patients often have small hands and feet, deceleration of the rate of head growth, and repetitive, stereotyped hand movements. Many patients have seizures, have no verbal skills, and cannot walk. Scoliosis and constipation are prevalent. Despite severe disabilities, affected women can live up to 40 years of age.
The diagnosis is made after clinical presentation and detection of a genetic mutation. EEG and motor abnormalities can be detected from symptom onset. Currently, there is no available treatment.

Huntington's disease

Huntington's disease (also known as Huntington's chorea) is a rare autosomal dominant genetic disease with the classic triad of symptoms: movement disorders, cognitive disorders, and psychiatric abnormalities.

The cause of the disease is a CAG trinucleotide repeat expansion in the huntingtin (HTT) gene. The mutated gene product has a toxic effect leading to brain atrophy, particularly affecting Gaba-ergic nerve cells in the basal ganglia; above all, medium-spiny neurons in the corpus striatum are damaged.

Symptoms usually appear between the ages of 35 and 50, correlating inversely with the number of repeats (the more CAG repeats, the earlier the onset). The earliest symptoms are subtle changes in mood and mental abilities, followed by a lack of coordination and unsteady gait. As the disease progresses, choreatic movements like fast, involuntary spasms of the face and the distal parts of the extremities become more evident. Later symptoms include involuntary hyperkinesia, psychotic symptoms, and eventually dementia. Physical abilities gradually worsen until the patient can no longer talk and walk. Once diagnosed, patients live ten to twenty more years, on average. The definitive diagnosis is made after detecting the trinucleotide repeat expansion in the HTT gene, e.g., PCR.

Currently, there is no causal therapy available. However, certain medications can reduce hyperkinesis, or antidepressants can alleviate the psychiatric symptoms.

Duchenne muscular dystrophy (DMD)

Duchenne type muscular dystrophy is the most common disease in the group of progressive muscular dystrophies, characterized by primary muscle fiber degeneration. Muscle cell death in DMD is caused by a gene defect on the X chromosome in the dystrophin gene, making the muscles vulnerable to oxidative and mechanical stress. The degenerated muscle fibers are sometimes replaced by adipose or connective tissue so that swelling occurs, and the muscle atrophy is not obvious. This process is called pseudohypertrophy.

The typical onset is between the first and the fifth year of life, leading to a rapid paresis and muscle atrophy beginning from the pelvic girdle, progressing to the shoulders. Until the age of 13, the patients are unable to walk alone, becoming paralyzed from the neck down. Due to cardiac or pulmonary insufficiencies, the patients usually die within 20 years.

DMD affects about one in 5000 males at birth. Women are usually the source of inheritance because they have two X chromosomes. A muscle biopsy usually makes the diagnosis.

No treatment exists yet for Duchenne muscular dystrophy. Nonetheless, medical and supportive treatments can reduce morbidity, improve quality of life and prolong lifespan.

Tourette's syndrome

Tourette's syndrome (originally called Gilles-de-la-Tourette syndrome) is a common neurological disorder with unknown etiology. As a higher familial incidence is observed, a genetic link is presumed, but the involvement of a specific gene has not yet been proven.

The syndrome is characterized by multiple motor and vocal tics, i.e., repetitive actions that can only be suppressed to a certain degree. They may affect the face, neck, and shoulder or may cause vocal automatisms, including echolalia (obsessive repetition) or coprolalia (shouting obscene words). The severity of tics may wax and wane and usually persist for more than one year after the onset.

Men are more commonly affected than women. The condition is normally diagnosed during early childhood, but patients experience peak tic severity before 18 years of age. The condition often improves after this time. The syndrome is often associated with an attention-deficit-hyperactivity-disorder (ADHD) or other psychiatric disorders, like obsessive-compulsive disorder.

Treatment is based on medication, behavioral therapy, and social skills training.

Diseases of the peripheral nervous system

Myasthenia gravis

Myasthenia gravis is an autoimmune disease in which mistakenly produced antibodies block and destroy postsynaptic acetylcholine receptors (nAChRs). This disrupts the neuromuscular transmission at the motor endplate, resulting in exercise-dependent muscle weakness. The muscle weakness worsens with activity and improves with rest. In most cases, myasthenia gravis is associated with a pathological change in the thymus. The thymus is an organ of the immune system where T cells mature. The changes there probably lead to the development of T helper cells against the nAChRs, which can initiate antibody production in B cells.

The eye, face, and swallowing apparatus muscles are most commonly affected. Double vision, drooping eyelids, speech, and walking problems may occur.

EMG fatigue tests can be used to confirm the diagnosis.

Treatment is based on the use of immunosuppressants and cholinesterase inhibitors, and thymectomy (removal of the thymus) is sometimes effective. Spontaneous remissions sometimes occur.

Peripheral neuropathy

Peripheral neuropathy is a disease of the peripheral nervous system (PNS) with systemic causes (e.g., toxic, infectious, or metabolic factors). Symptoms often include pain, sensory loss, paresis, and autonomic dysfunction, as motor, sensory and autonomic nerves can be affected. The disease usually affects the longest nerves first, so the most common initial sign is numbness in the toes.

In Europe, diabetes mellitus (*diabetic neuropathy*) and alcohol dependence are the most common causes; in tropical and subtropical regions, it is malnutrition and leprosy.

In addition to good medical history, EMG can be used for diagnostics. Therapeutically, the causing disease must be treated.

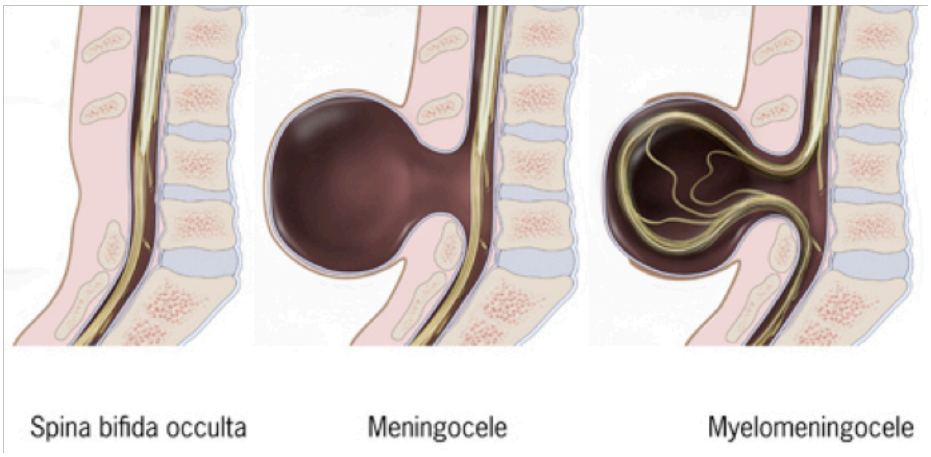
Non-genetic developmental disorders

Certain developmental insults can cause devastating damage to the developing brain and spinal cord. These include vitamin deficiency (neural tube defect), alcohol (fetal alcohol syndrome), iodine deficiency, and infections (rubella). Each one of these can cause widespread damage to the fetal brain. It is possible that viral infections may also cause cerebral palsy during pregnancy.

Neural tube defect (NTD)

Neural tube defects are the most common malformations of the brain and spinal cord. Neural tube defect results from a disruption of the very early development of the neural tube, with incomplete closure at the rostral and caudal ends. The most common result of an incomplete closure is seen in the caudal part of the spinal cord, where it is called spina bifida. Depending on how severe the closure defect is, one distinguishes between different forms (see figure).
Usually, the damage to the spinal cord results in paralysis of the lower limb and loss of control of the bladder and bowel. Cases affecting the rostral neural tube can result in malformation of the brain ventricles, resulting in hydrocephalus.

Some families have a genetic predisposition to NTD. However, the most critical factor has been shown to be a lack of vitamin folate. For this reason, all women who might possibly become pregnant should make sure that their folate intake is high – either by eating leafy vegetables and other folate-rich foods or by taking folate vitamin tablets as a supplement. In many countries, bread flour and breakfast cereals are enriched with folate to ensure that the whole population has adequate folate levels.



Spina bifida aparta (Myelomeningocele): ***at the point where the spinal cord is not fused, the spinal cord and the meninges protrude, forming a sac enclosing all spinal elements;***
Spina bifida cystica (Meningocele): ***the meninges herniate between the vertebrae creating a cyst;***
Spina bifida occulta***: the neural tube is closed correctly, but the vertebral arches are not merged.***

Congenital rubella

During the first three months of pregnancy, rubella infection (German measles) can cause significant brain abnormalities, including deafness and blindness.

Iodine deficiency

Iodine deficiency during fetal development is probably the most important cause of mental retardation worldwide. It affects millions of children in mountainous areas of Asia and South-East Asia, where iodine has been leeched out of the soil. Iodine deficiency results in hypothyroidism that permanently damages the developing brain. The problem of iodine deficiency is easily remedied with the supply of iodine supplements in salt and oil, but this is not always easy to achieve because of logistic impediments.

Infantile cerebral palsy (CP)

Infantile cerebral palsy refers to a group of movement disorders in early childhood. The main cause appears to be damage to the striatum and pallidum ('basal ganglia') in the last three months of pregnancy, possibly from an infectious agent. Because the cerebral cortex develops after birth, it usually escapes damage in cerebral palsy cases.
Four subtypes of CP are distinguished:

- spastic (most common, characterized by increased muscle tone);
- ataxic (lack of coordination of movement);
- athetoid (involuntary, slow movements of the extremities);
- mixed.

There is no cure for cerebral palsy. The goal of treatment is to help the person be as independent as possible.

Psychiatric disorders and disorders of behavior

Many neurological diseases are reasonably well understood in terms of the specific brain regions that are affected. However, in the case of mental illness, the situation is much less clear. While the treatment of mental illness has improved a great deal in the past 50 years, there has not been much progress in understanding the underlying pathological changes that cause these conditions. Mental illness affects about one-third of all people at some point in their life.

Attention deficit hyperactivity disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by signs of inattention, hyperactivity, and impulsivity appearing outside our social norms. These symptoms must occur over at least six months and have to be observed in different environments (typically school and home) for a diagnosis.
While the condition is usually diagnosed in children, it can persist into adult life. There are considerably more boys than girls affected. The incidence of ADHD in children is estimated to be around 5% worldwide. For many years there has been controversy about the diagnosis and treatment of ADHD. However, there is now an international consensus that stimulant medication (methylphenidate) effectively reduces symptoms and makes it possible for the individual to live a normal life.

Autism spectrum disorder (ASD)

The term autism spectrum disorder refers to a range of developmental conditions, including problems with social communication and unusual repetitive behavior. Although autism is one of the best-known child psychiatric terms, the disorder is rare overall. Classical (early-childhood) Autism or Asperger syndrome are examples of this group of diseases. The symptoms differ depending on which subtype the patient is affected by. As a rule, however, these are accompanied by disturbed social behavior and an inability to empathize. The classic variant is usually accompanied by cognitive impairment, but Asperger's syndrome is not necessarily. Insular gifts, as seen in films, are extremely rare and a subtype of Asperger's syndrome. The cause is still unknown. Several genes are associated with an increased risk of the disease.

> *A Lancet study from 1998 by Andrew Wakefield claimed to have shown that vaccination against mumps, measles, and rubella was involved in the development of autism. Because Andrew Wakefield received dubious payments in the run-up to publication and misrepresented results, the study was officially retracted by the Lancet in 2010. Andrew Wakefield was banned from practicing in England, where he had previously been a doctor. Although enormous resources were devoted to it, no subsequent study could reproduce his results.*

Affective disorders

Affective disorders are a group of psychological disorders, all featuring a clinically significant change in mood. They can be divided according to their so-called polarity and the time course. The polarity indicates the direction in which the mood change takes effect. Examples are depression (pathological decline in the mood) or mania (pathological increase in the mood). If the change is only in one direction, it is called a unipolar disorder. If the mood is sometimes elevated and sometimes depressed, we speak of a bipolar disorder. The most common affective disorder is unipolar depression, i.e., a disorder characterized by a depressed mood without phases of euphoria or similar.

Unipolar depression

Depression is a state of low mood and lack of interest in everyday activity. Symptoms may include changes in appetite or sleep patterns, loss of energy, decreased libido, irritability, feelings of worthlessness, and thoughts of suicide.
There is no single cause of depression, but it is associated with many factors, including family history, trauma, and stress. Neurotransmitter imbalance is thought to underly many cases of depression. Despite numerous studies, the exact neurotransmitters involved in depression are still unknown. Current pharmacological treatment primarily aims to increase the activity of the neurotransmitter serotonin in the brain. This is achieved either by decreasing uptake (selective serotonin reuptake inhibitors – SSRIs) or increasing production. Several different drugs are currently prescribed, with varying efficacies and side-effect profiles. The real value of pharmacological treatment in cases of mild-to-moderate depression has been questioned, and there is a great deal of current interest in the use of cognitive-behavioral therapy.
Significant depression affects a third of the population at some point in their lifetime. The episodes generally begin in early adulthood. Women are recorded as being more commonly affected, but this may just represent a greater willingness of females to seek help.
The diagnosis is mainly due to the clinical presentation. Sometimes a higher rate of REM sleep can be observed.

Bipolar affective disorder

Bipolar affective disorder is defined by the presence of one or more major episodes of abnormally elevated mood. These elevated states are clinically referred to as mania. It is common for individuals who experience manic episodes to experience depressive episodes as well, hence the name 'manic depression. Because of these changes in both directions of mood distortions, it is called a bipolar affective disorder. The cause is still unknown, but there is a tendency for cases to cluster in families.
Some pharmacological and psychotherapeutic techniques have been applied to treat bipolar affective disorders. However, the mainstays of treatment are mood stabilizers such as lithium chloride (which affects intracellular calcium handling) or sodium valproate (which affects neurotransmission).
It is crucial to distinguish between depression and bipolar disorder carefully. Medications for (unipolar) depression can quickly move a misdiagnosed bipolar disorder from the depressive phase to a very strong manic phase.

Schizophrenia

Schizophrenia is a psychotic illness characterized by abnormalities in the perception or expression of reality. It is a severe and frequently chronic illness that often first appears in late adolescence. Schizophrenia affects approximately 1% of the population and is the single largest cause of admissions to mental hospitals in western countries. It also accounts for the largest proportion of permanent residents in such institutions because it often results in severe levels of impairment. Depending on which symptoms predominate, different subtypes can be classified. The most common is paranoid schizophrenia, mainly characterized by (auditory) hallucinations and delusions. However, schizophrenia can also be accompanied by experiencing flattened affect (decreased emotional responsiveness), apathy, and withdrawal from society.

It is currently suspected that the disease is multifactorial, i.e., that it is caused by a combination of genetic and environmental factors, such as infections during pregnancy or high-dose cannabis consumption in childhood and adolescence.

There has been a great deal of research into the particular brain regions and neurotransmitters involved in the disease, but we still do not have a clear picture of the underlying pathology. However, drug treatment is moderately effective in many cases. Some of these drugs work by influencing the level of neurotransmitters such as serotonin and dopamine.

Obsessive-compulsive disorder (OCD)

OCD is a neurotic disorder characterized by obsessions or compulsions, or both. Obsessions are recurring, intrusive thoughts that invade a person's consciousness and produce anxiety. Common obsessions include worries about contamination from germs, thoughts about committing violent acts, and constant doubt. Compulsions are repetitive behaviors or thoughts triggered by anxiety. Compulsions accompany obsessions in about 80% of cases and are usually simple acts such as washing, checking, or counting. OCD affects between 2% and 3% of the general population and occurs equally common in males and females. The precise areas of brain dysfunction have not yet been found. Neurobiologically, it is assumed that there is a dysbalance in the regulatory loop between the frontal brain, limbic system, and basal ganglia.

Selective serotonin reuptake inhibitors (which are used in the treatment of depression) have been found to markedly reduce the symptoms of OCD in about 60% of patients. The success of this drug has led to the suspicion that OCD could arise from the disruptions of neurotransmitter systems.

Substance abuse

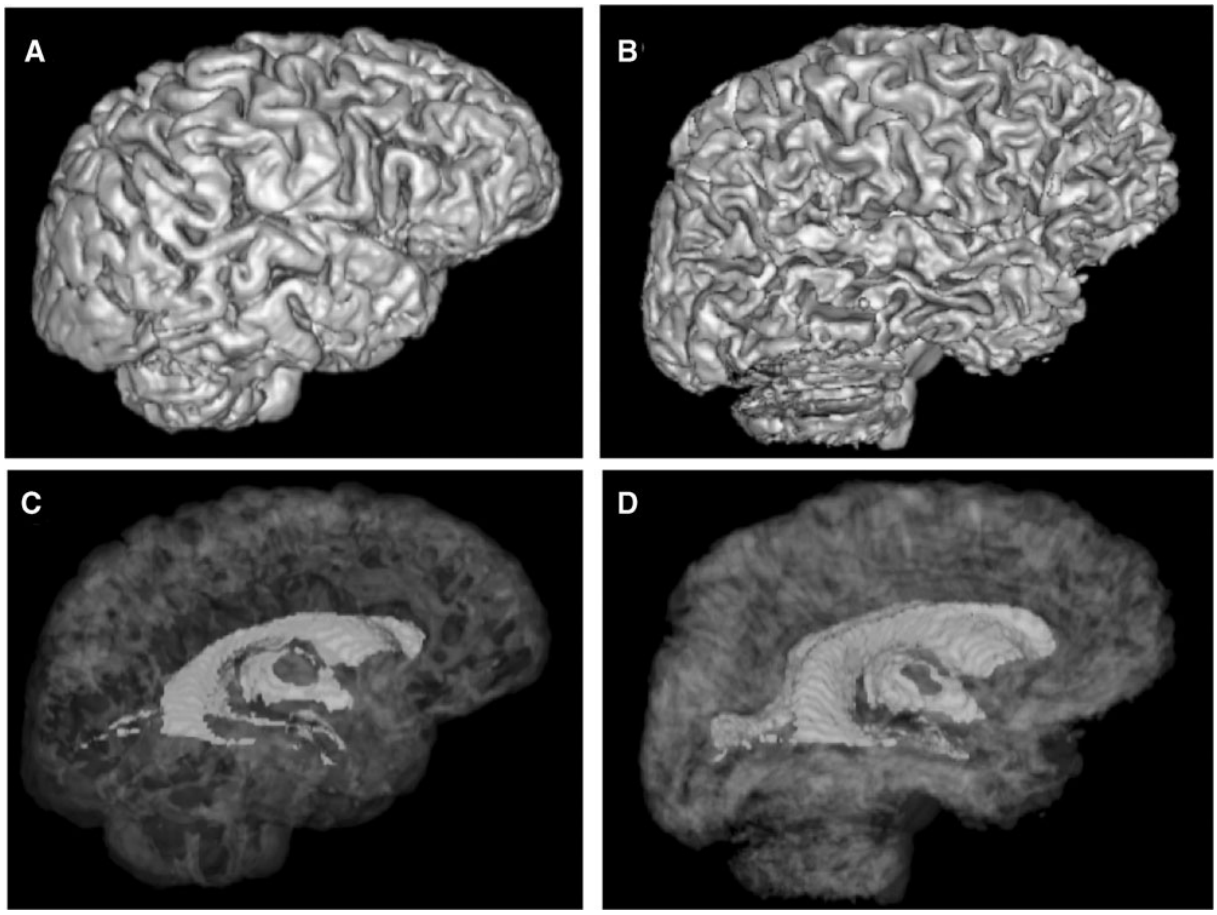
Substance abuse can be defined as the abnormal use of a substance that leads to impairment of the physical, social, or occupational aspects of one's life. Substance abuse often leads to dependence or tolerance. Dependence is the physical need to use a drug to maintain the effects provoked by its intake. Dependent users experience withdrawal symptoms when they are unable to maintain consumption of the drug. Addicted users crave the drug even if they know it damages their work, health, and family. Drugs at higher risk of dependence are cocaine, heroin, and nicotine; drugs with lower risk are alcohol, cannabis, ecstasy, and amphetamine. During the development of dependence, the body and brain slowly adapt to the repeated presence of the drug, the lack of which then causes unpleasant feelings.
Tolerance to a drug is experienced when a specific dose, taken previously to generate a certain physical state, is no longer effective, and higher doses are required. With regular use, tolerance may develop. Higher doses or more frequent use are needed to produce the same level of pleasure and relief from withdrawal.
The main groups of substances of abuse are:

- stimulants: including caffeine, amphetamines, cocaine, and nicotine. The intake of stimulants leads to heightened alertness, agitation, improved mood, increased heart rate, reduced appetite, and increased aggressive behaviors.
- sedatives: including alcohol, barbiturates, and benzodiazepine tranquilizers. They produce sedation, sleep, behavioral disinhibition, and a decrease in anxiety.
- opiates: including heroin, oxycodone, and morphine.
- hallucinogens: including LSD, phencyclidine, bromocriptine, and cannabinoids.

In most cases, addictive substances can generate feelings of pleasure by acting on the dopamine reward pathway from the ventral tegmental area to the accumbens nucleus.
The primary goal of therapy is abstinence; if this is not possible, a reduction in consumption is sought.

Wernicke-Korsakoff Syndrome (WKS)

Both Wernicke's encephalopathy and Korsakoff's syndrome are now considered as clinical variations of the same disorder. Wernicke's encephalopathy refers to the acute form, and Korsakoff's syndrome is the chronic condition. The underlying cause is a lack of thiamine (Vitamin B1), usually due to malnutrition as a consequence of alcohol abuse. Because of the high-calorie content of alcohol, severe alcoholics do not need much more food to reach their daily caloric needs and thus fail to meet their vitamin needs. The absence of thiamine interrupts carbohydrate metabolism, leading to various neuronal and vascular damage, including demyelination, glial and neuronal cell death, and small hemorrhages.
The most prominent symptom of WKS is the failure to form new memories. Patients may recall events from the distant past but cannot recall what they had for breakfast. A characteristic feature of the memory loss is the invention of information to fill memory gaps – called confabulation.
Laboratory diagnostics can detect a vitamin B1 deficiency. A corpora mammillaria's atrophy can usually be diagnosed with MRI, explaining the inability to form new memories.
It can be treated by high-doses vitamin B1 supplementation. Patients with acute Wernicke-encephalopathy usually continue to have a chronic Korsakoff-syndrome.
The prognosis is poor, and about 20% die some weeks after diagnosis.



Surface rendered brains (top) and rendered ventricular system (bottom, green) of a 59-year-old healthy man (A and C) and a 53-year-old man with WKS (B and D). Note the shrinking of the cortical gyri and widening of the sulci (B) and expansion of the ventricles (D) of the WKS compared with the control (A and C).; *Sullivan, Pfefferbaum, Neuroimaging of the Wernicke–Korsakoff Syndrome, Alcohol and Alcoholism, 44;2-2009:155–165.*