Neuroaesthetics, lecture 2, spring 2013:

Basic neuroanatomy and neurophysiology

So far, we have not focused on the anatomy of the brain and the nerve cells. (**slide 3**) On the macro-anatomical level, the brain consists of two hemispheres containing the same anatomical structures. Nevertheless, the two hemispheres are far from identical. For instance, the main language areas are localized in the left hemisphere. The brain which you can see here is seen from behind, toward the protruding occipital lobes, where the primary visual cortex is localized.

We see that the brain is strongly folded. This is a characteristic of the brains of advanced *Mammalia*, and, particularly of *primates*: that is the apes and the humans. The folding of cortex is the only way to keep with the fact that complex cognition requires large areas of cortex, restricted to 1.350 ccm, the volume of our scull. The folding organizes the brain surface into *gyri*, which is plural for gyrus, and *sulci*, plural for sulcus, where the gyri is mounting on the surface, and the sulci are the grooves between them (**next**)

When the early anatomists dissected the brain they found that the outer surface was gray, covering an inner, so called white substance. We still use the words white and gray substance to designate the two layers. The white substance is white because it consists of large bundles of nerve fibers, where most of the fibers are encapsulated in so called neuroglia, cells that are wrapped around each nerve fiber, and, hence, provide them with an insulating layer of fat.

We will return to the physiological necessity of this fat in electrical nerve-impulse transmission (**next**) later in the present lecture. Gray substance is grey because it consists of the so called nerve cell bodies, the genetic and ´administative` area of the cell (cf. **slide 42**, below). The gray substance is found in the cortical areas of the brain.

Bundles of nerve fibers cross from one hemisphere to the other through the so called *commissures*. In this slide you can see the large *corpus callosum*, which means “hard body”, and the *anterior commissure*. The crossing fibers connect corresponding gray substance areas in the two hemispheres.

We will take a closer look at the macro anatomy of the brain (slides **36-37**).

The most conspicious sulci divide the brain into separate lobes. We have the frontal lobe, the parietal lobe, the occipital lobe, and the temporal lobe, with their respective cortical and sub-cortical structures. The central sulcus separates the somatosensory areas in the *postcentral gyrus* from the motor areas in the *precentral gyrus*.

How have these structures evolved? To answer this question we will take a closer look on the differences between the brains of amphibians, reptiles, primitive Mammalia, and progressive Mammalia, including the primates, to which we belong. In the modern amphibians (look at slide, Fig. 418. B) the gray matter is located deep to the brain surface, and consists of the so called basal nuclei (b), the paleopallium (p), and the archipallium (a); (the two last-mentioned correspond to the mesocortex and the allocortex (cf. below)). In a more progressive stage (C) the basal nuclei has moved

inwards, and are located on the lower, or ventral, side of the brain. Bundles of fibers connect, in a reciprocal manner, the *thalamus*. In a more advanced reptilian stage (D) a small part of cortex has a six cell-layered structure; hence, this marks the appearance of the neopalluim, or neocortex. In E, you can see a primitive mammalian stage, where the neopallium occupies the superior surface of the brain, separated from the paleopallium by the rhinal fissure. The ventrally located paleopallium becomes a primary olfactory cortex. The archipallium is folded to become the hippocampus. In advanced mammalia (F), like the primates, the neocortex covers almost all the brain surface, and has become strongly folded. Still, there is a rest of the paleopallium located ventro-medially, and which is a part of the olfactory brain, and connected to the limbic system. Dorsomedially, we can see that the archipallium is folded to become the hippocampus, which is also a central part of the limbic system (above).

The cerebral cortex has been investigated (**next: slide 47**) in micro details by Korbinian Broadmann (1909/60). He studied every patch of cortex in the microscope. His interest in cell morphology and cytoarchitecture, that is how cells are arranged with respect to each other within an area, resulted in a division of the brain into approximately 52 regions. His method used for staining brain tissue for preparing microscopic sections will be a subject for the ultimate part of the present lecture.

On this slide you can see the different sensory inputs to the brain, and the motor output: We have the somatosensory inputs from the different sense organs of our skin ending in the somatosensory cortex in front of the central sulcus; we have the visual input to the primary visual cortex in the occipital lobe; the auditory inputs terminate in the temporal lobe; the

olfactory and the gustatory stimuli which trigger activation in the medial part of temporal lobe. Finally, we have the motor cortex, from which the motoric signals run through the motoric nerves down the spinal cord, where they are connected to a second set of neurons which lead to those muscles that are under our conscious control. (next)

The somatosensory and the motoric cortices are located on each side of the central sulcus; the motor cortex anterior to the central sulcus and the somatosensory cortex posterior to it. Motor cortex has Brodmann number 4, while somatosensory cortex includes Brodmann areas 3, 1, and 2. This slide shows areas in the motor and somatosensory cortices concerned with particular areas of the body. The reason why the head and the arm, the tongue and the swallowing apparatus occupy a larger part of the cortices is that a much greater control is required, for instance, to move our fingers than our toes; mind, … how you would react to a dentist who controls the drill with his feet?

(go to slide 45) The descending nerve fibers from the motoric cortex cross the midline; they control the contralateral part of the body. The ascending, somatosensory fibers will also cross the midline ascending towards somatosensory cortex on the contralateral side of the brain.

Karl Kleist (1879–1960) was a German neurologist who made notable advances in descriptive psychopathology and neuropsychology. Localization of function in the cerebral cortex of man included mapping of cortical functions on brain maps. The work is based on several hundred cases of shot wounded patients of World War I, whose function-deficits Kleist deliberately studied and described in detail during their lifetime. Later on, after their death, by means of

brain autopsy he documented the lesions and was, thus, able to localize brain function in each single case. The functional map of Kleist is very close to the cytoarchitectonic map of Brodmann.

(next slide: **38**) The lobes of the brain are further sub-divided into special areas with particular function, and particular nerve architecture. For instance, the frontal lobe includes such areas as the *prefrontal cortex* and the *orbitofrontal cortex.*

We shall particularly notice the orbitofrontal cortex, since it plays a central role in the perception of beauty, be it an artwork, music, a face etc., as has particularly been demonstrated by Semir Zeki's group in London (cf. lecture one, and lecture three). So this structure will stand in the very focus of this series of lectures. The orbitofrontal cortex is part of the so called limbic system, consisting of phylogenetic old structures that constitute our emotional nerve network. We will return to the system later in this lecture, as well as later in my series of lectures. (**next: slides 39-40**)

Kleist has labelled a part of the frontal cortex the "*efficiency of thought"*, localised within the frontal cortex, Brodmann area 10. The frontal lobe is concerned with advanced cognitive processes, such as decision making.

The medial part of BA 10 is activated if we make judgments about what is morally good, what function best in social settings, as well as when we make aesthetic judgments. In short, the prefrontal cortex is involved in complex aspects for planning and execution of behavior.

Thomas Jacobsen's research group in Leipzig, Germany, carefully designed an experimental paradigm that enabled them to demonstrate that the neural networks for the aesthetic ***judgment*** task overlapped with those working during moral and social judgments. The aesthetic judgment is a cognitive process relying on a network of reasoning; this network is localized in the medial prefrontal cortex, within Brodmann's areas 9 and 10 (BA9 and BA10). This shows that our brain, in fact, works according to the Greek word kalokagatia, telling that what is beautiful is also good, which dominated the classical aesthetics as well as that of the Middle Ages. This means that the ugly is identical with the evil, as you can see on this slide of a Norwegian altar frontal of the 13th c., at Bergen Museum, where the torturers are casted into brutalized caricature.

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My next topic will be the visual system. Look at this painting by Richard Anuzkiewic's. … Can you see how it almost vibrates before our eyes. But what happens if we convert it into grayscale?

We will try to explain this feature physiologically. First we will take a brief review of the physiology and anatomy of the visual system.

The primary visual cortex corresponds to Broadman area 17, or, simply *BA 17*. (**next**) Another name of it is *striate cortex*, because of the stripes that are found in this part of cortex

when studied in the microscope. Still another name of it is *V1* (visual 1), which tells us that this is the primary visual cortex.

In the Figure 6.3 on this slide (**: slide**), you can see a tracing of the visual pathways. Nerve fibers from the nasal part of the retina cross the midline in the optic chiasm, entering the *thalamus* complex in a nucleus called the *lateral geniculate nucleus*. The fibers from the temporal part of the retina go uncrossed to the lateral *geniculate* nucleus. What this implies is that information from the right visual field projects to the left side of the brain, while information from left visual field is sent to the right half of the brain.

From the lateral geniculate nucleus, the information is sent, by a second set of neurons, to the primary visual cortex in the occipital lobe (BA 17, V1, cf. above). Let us now take a look at an interesting artwork, Eduard Monet's *Soleil levant*, the Sunrise, from 1872, and we will now use this artwork to demonstrate how our brain deals with visual input. (**next: slide 51**)

In the grayscale version of Monet's *Soleil levant* (1872) the intensely bright sun has almost completely disappeared. Why? The reason is that this sun is isoluminant with the background colour. But why is the sun so intensely shimmering when we look at the original painting?

The reason is that there are two different systems leading from the primary visual cortex to higher visual areas of the brain. The «where system» which follows the bundle of nerve fibers called the *superior longitudinal fasciculus* is colour blind and only tuned to luminance contrasts. The ventral «what system» follows the *inferior longitudinal fasciculus*. It is colour

sensitive, and have particular centers for recognizing objects, faces etc. The colour sensitive «what» pathway recognizes the sun and its colour in Monet's painting. The «where» pathway is, however, blind for the isoluminant sun. This leads to an oscillation between the «what» and the «where» system, which results in a shimmering of the sun. (**next**)

And it is precisely the same effect that is at work when we look at Richard Anuzkiewic's *Plus reversed* (1960), with its vibrating red patches.

The process of identifying the parts of the brain that are involved in language began in 1861, when Paul Broca, a French neurosurgeon, examined the brain of a recently deceased patient who had had an unusual disorder. Though he had been able to understand spoken language and did not have any motor impairments of the mouth or tongue that might have affected his ability to speak, he could neither speak a complete sentence nor express his thoughts in writing. The only articulate sound he could make was the syllable "tan", which had come to be used as his name.

When Broca, after Tan's death autopsied his brain, he found a great lesion in the left inferior frontal cortex. Subsequently, Broca studied eight other patients, all of whom had similar language deficits along with lesions in their left frontal hemisphere. This led him to make his famous statement that "we speak with the left hemisphere" and to identify, for the first time, the existence of a "language centre" in the posterior portion of the frontal lobe of this hemisphere. Now known as Broca's area, this was in fact the first area of the brain to be associated with a specific function — in this case, language.

Ten years later, Carl Wernicke, a German neurologist, discovered another part of the brain, this one involved in understanding language, in the posterior portion of the left temporal lobe. People who had a lesion at this location could speak, but their speech was often incoherent and made no sense.

Wernicke's observations have been confirmed many times since. Neuroscientists now agree that running around the *lateral sulcus* (also known as the fissure of Sylvius) in the left hemisphere of the brain, there is a sort of neural loop that is involved both in understanding and in producing spoken language. At the frontal end of this loop lies Broca's area, which is usually associated with the production of language, or language outputs . At the other end (more specifically, in the superior posterior temporal lobe), lies Wernicke's area, which is associated with the processing of words that we hear being spoken, or language inputs. Broca's area and Wernicke's area are connected by a large bundle of nerve fibres called the *arcuate fasciculus.*

Broca’s area, which has number 44 in Brodmann’s system, is the same area where there has been found a substantial network of mirror neurons, within the ventral premotor cortex.

Last lecture we saw that if an ape is looking at a man executing a grasping movement, in the brain of the ape the mirror neurons will be activated. The same neurons will be activated if the ape is doing a corresponding grasping movement. The activation of the mirror neurons will, however, not result in a real movement. What they do is to react *“as if”* in movement, leading to our understanding of a movement executed by others. Significantly, this motoric understanding also leads to an activation of our emotional nerve networks, leading to empathic responses to what we see; the importance of the mirror mechanisms is that they

enables us to understand mechanisms in what we may designate as our “empathic network” in the brain.

When observing movements of others our brain “mirrors” the movements (**next**), as in this dramatic art performance; but also when we watch a ballerina, our brain mirrors *her* movements. (**next**) This mirror mechanism are localized in the *prefrontal cortex* and in the *posterior parietal cortex,* as you can see on the brain to the right in this slide. (**next**)

The asymmetry of the language areas, its lateralization to the left, and its co-localisation with the mirror neuron system, has led to some speculation whether the mirror mechanisms are also left lateralized. Recent studies (Aziz-Zadeh et alii, 2006) has, however, documented that the mirror neuron system is not lateralized to left hemisphere, and concludes that the mirror neurons in BA 44 is not a precursor to the development of lateralized language function in humans. Still, one can ask whether the mirror system and the language mechanisms are interconnected in some manner. One possibility is that since speech involves specific motoric actions to move the jaws, precise control of such movements might be learned through observation. If this holds true, this may indicate that mirror neurons in Broca’s area aid in acquisition of novel movement patterns required for speech (D. R. Lametti and A.G. Mattar, Mirror Neurons and the Lateralization of Human Language, The Journal of Neuroscience, June 21, 2006, 6666-6667)..

The parietal lobe includes neural networks for complex recognition of form, such as 3D; also the brain's symmetry network is partly localized within the parietal lobe, partly in the occipital lobe. Moreover, there is a network of mirror neurons in the posterior parietal cortex. Activation of *parietal regions* for symmetric stimuli brings support to the ideas that the aesthetic experience is characterized by *visuo-spatial coding* as well as, importantly, by *motor mapping*, i.e. a function executed by mirror neuron activation. In fact, there is now consisting evidence that the *posterior parietal* cortex, including the *intraparietal sulcus,* and the *ventral premotor cortex* is part of a motor system, playing a fundamental role in *visuomotor transformation, spatial recognition* and *processin*g.

When we try to grasp a 3D form, there will be an activation of Brodmann area 7 in the parietal cortex. This means that when we look at sculptures, such as this one by Henry Moore, our parietal lobe both mirrors its frozen movement, and tries to interpret its depth for us, so that we can calculate how it is sculptured around, also at the side that is obscured by our present position.

In fact, this system also works when we look at paintings, particularly when the paintings have «soft edges», so that they are not clearly delineated. Our Brodmann area 7 in *parietal cortex* tells us how to recognize the three dimensional form in such more sketchy paintings.

Experimentally, it has been proved that when we analyze a 3D form, comparing it with another 3D form, trying to find out whether the two forms are equal, a process called mental rotation, the foremost activation takes place in the parietal cortex, Brodmann area 7.

There are sex-differences here: men are usually more clever in mental rotation tasks than women. Women, on the other hand, are much more clever in a verbal description, telling how different items are located in relation to each other etc. The differences betwee sexes is usually explained according to the so called hunter gatherer hypothesis, where men were out in landscape, hunting, while women were home, gathering berries, fruits, preparing food etc.

The limbic system is the set of brain structures that forms the inner border of the cortex. (**slides 53-55**) The components of the limbic system located in the cerebral cortex generally have fewer layers than the classical 6-layered neocortex, and are usually classified as (**slide 56**) allocortex (= archicortex), and the mesocortex.

The cerebral cortex consists of the <u>neocortex,</u> meaning <u>new cortex</u>, consisting of
sensoric, motoric, and association areas

mesocortex
consists of the so called paralimbic areas,
including the *cortex cinguli, parahippocampal gyrus, cortex insula,*
and the *orbitofrontal cortex.*

Both cortex cinguli and the insula are activated during feeling of disgust, but also, in some cases, during feeling of pleasure, such as aesthetic pleasure. Disgust and pleasure activates, however, different parts of the cingulate cortex and the insula.

The role of the *orbitofrontal cortex* in beauty judgments, as recorded in the fMRI scanner, has particularly been stressed by Kawabata & Zeki.

Moreover, Nakamura *et. al.* (1998) has found a correlated increased activation of the orbitofrontal cortex in a study where male subjects made positive attractiveness judgments of female faces.

A central role has been attributed to the orbitofrontal cortex in aesthetic judgments, as well as in contexts where reward mechanisms and social interaction, including moral judgments are prevailing.

The orbitofrontal cortex is one of the few areas that show consistent responsiveness to objects of both positive and negative valence. The orbitofrontal cortex is perhaps primarily a higher-level sensory cortex for smell and taste, serving as a secondary olfactory and gustatory cortex. This may indicate something significant about the origins of aesthetics in the appraisal of food sources. An interesting example of activation of orbitofrontal cortex and the insular cortex is as response to the rating of attractiveness and goodness of faces. Faces that we rate as attractive will also be rated as good, and the more attractive, and good the rating is, the more is the activation of the orbitofrontal cortex. The inverse relationship for the insular cortex (T. Tzukiura and R. Cabeza, Shared Brain Activity for Aesthetic and Moral Judgments: Implication for the Beauty-is-Good stereotype SCAN (2011) 6, 138-148).

allocortex

Includes the *hippocampus*, and the *olfactory cortex*, which is the part of cortex receiving impulses from the olfactory bulbs.

Hippocampus is significant particularly for long time memory. It has been scientifically proved that repeated stimulation of the nerve fibers entering the gyrus dentatus leads to an enhanced and long lasting “memory” of this particular stimulation. The study goes as follows: send a stimulus in the nerves leading into the dentate gyrus and record the activity in

the cells that are stimulated. Then, send a “train” of impulses in the same bundle. Finally send a new single stimulus into the gyrus dentatus, and you will record a very strong response. This strong response to one single stimulus lasts for days.

Mesocortex and allocortex are parts of the so called limbic system

Paul Broca described this part of the brain *il grand lobe limbique*: the great limbic ring: cortex cinguli, hypothalamus, the anterior nuclei of thalamus, and the hippocampus form what is called the "classic limbic ring".

In the 1930s it was James Papez who first put forward the hypothesis that these structures were organized as a system of emotions. The limbic system was therefore also called "Papez circuit".

After these pioneering works, there has been intensive research on this system:

the amygdala, a network of nerve cells located anteriorly, i.e. in front of hippocampus is now considered to be one of the key structures of the limbic system, which also include the orbitofrontal cortex, parts of the basal ganglia, and more nuclei of the thalamus than was previously suggested.

But what about art and the emotional system? Vartanian and Goel (2004) investigated rating of paintings as *aesthetic preference* as viewed in the f-MRI scanner. Their results document rating according to a first-person point of view: i.e. *subjective states of experience*:

The data demonstrate that activation in cortical structures implicated in processing *emotion* or *reward* co-varied as a function of *preference rating*; particularly important is the activation of the *caudate nucleus* and the *cingulate sulcus,* structures included in the limbic system.

f-MRI data shoving positive evaluation : this is beautiful activates the left *cingulate cortex* and the right *nucleus caudatus.*

We will now take a closer look on the nerve cells, their anatomy as well as their function. We will start with a presentation of a very significant method to stain neurons, a method that revolutionized our insight into the anatomy of the central nervous system. This is the so called Golgi method after the Italian physician and scientist Camillo Golgi (1843–1926), who discovered it in 1873. It was initially named the black reaction - *la reazione nera* - but became better known as the Golgi stain or Golgi method.

Golgi's staining was famously used by the great Spanish neuro-anatomist Santiago Ramón y Cajal (1852–1934) to discover a number of novel facts about the organization of the nervous system, inspiring the birth of the so called “neuron doctrine”. Ultimately, Ramon y Cajal improved the technique by using a method he termed "double impregnation." Ramon y Cajal's staining technique, still in use, is called Cajal's stain.

Golgi's method stains a limited number of cells at random in their entirety. The mechanism by which this happens is still largely unknown. All parts of the cell are clearly stained in brown and black and can be followed in their entire length, which allowed neuro-anatomists to track connections between neurons and to make visible the complex networking structure of many parts of the brain and spinal cord.

Golgi's staining is achieved by impregnating fixed nervous tissue with potassium dichromate and silver nitrate. Cells thus stained are filled by a microcrystallization of silver chromate. Silver chromate (Ag_2CrO_4) is a brown-red crystal and is a chemical precursor to modern photography. It can be formed by combining silver nitrate ($AgNO_3$) and potassium chromate (K_2CrO_4): the silver chromate produced precipitates inside neurons and makes their morphology visible.

$$AgNO_3 + K_2CrO_4 = Ag_2CrO_4 + KNO_3$$

Ramón y Cajal said of the Golgi method:

“I expressed the surprise which I experienced upon seeing with my own eyes the wonderful revelatory powers of the chrome-silver reaction and the absence of any excitement in the scientific world aroused by its discovery.” (Recuerdos de mi vida, Vol. 2, Historia de mi labor científica. Madrid: Moya, 1917, p. 76.). In this slide you can see the so called Pukinje cells in cerebellum, stained by Cajal, using Golgi’s method. Here in a drawing by Cajal, 1888, directly after the microscope.

The neuronal organization of the retina puzzled students of vision for centuries, long before the microscope was enlisted to observe its intricate connections. The illustration combines one of the most beautiful early representations of its microscopic structure with the anatomist who produced it.

Tartuferi published the coloured illustration of the retina in 1887; his portrait is based upon a photograph from the archives of the University of Pavia, where he worked.

Tartuferi was a student of Golgi. The power of the silver chromate staining was initially demonstrated on the barbarizations of Purkinje cells in the cerebellum, but interest soon shifted to the retina where it was first applied by Tartuferi. In his diagram the horizontal and amacrine cells are clearly represented, as are the rods, cones and bipolar cells. Despite the detailed representation of the constituent parts of the retina, Tartuferi retained Golgi's view that the nervous system was a interconnected and continuous unit, a reticulum.

The structure of the retina had been speculated upon and examined microscopically long before Tartuferi's diagram was printed, but without the advantages that the silver staining method conferred. It remains an enigma that Tartuferi adhered to his mentor's reticular conception of the nervous system despite producing such a beautiful illustration of the individual elements in the retina.

Another great neuro anatomist was the Norvegian Fridtjof Nansen. Nansen is, however, better known as the philanthropic, saving thousands of Armenian refugees when they were persecuted by the Turks. He is also famous for his polar expeditions. Nansen spent a relatively short period as a neuroscientist but he made his mark during the years of his doctoral research. After completing his studies at the University of Oslo, he conducted his research as curator of zoology at Bergen Museum. His initial frustration with cell preparations resulted in him travelling to see Golgi and to learn the technique of the black reaction.

On his return to Bergen he applied the stain to vertebrate and invertebrate nervous systems, culminating in his thesis The Structure and Combination of Histological Elements of the Central Nervous System (1887). His portrait is combined with Plate XI from his thesis. The

beautifully detailed drawings were chromo-silver stained nerves from the spinal cord of hagfish.

Nansen was a staunch supporter of Ramon y Cajal's nerve theory as opposed to Golgi's reticular concepts, largely because he could not envisage how unipolar nerve cells could be accommodated in a reticular theory.

A nerve cell consists of the so called cell body, or *soma*, in which the cell nucleus, containing the DNA twisted into chromosomes, is being located. The cell body also contains the synthesis apparatus for proteins, such as enzymes, structural proteins for the cell skeleton and many other sorts of proteins and peptides (small proteins, those with very few amino acids).

Radiating from this cell body are multiple dendrites, receiving inputs from a vast number of other nerve cells; leaving the nerve cell body is a single axon, which, in some nerve cells, is very long, leading from the brain to the spinal cord, while it, in other nerve cells may be very, very short. It is the connection between different types of nerve cells that constitute what we call the neural networks, including many different centers of the brain. (**slides 9-14 show the Purkinje cells in the cerebellum at different levels of magnification and in different layers of the microscopic preparation; slides 15-16 show a cell in the cerebral cortex**).

But how does one nerve cell communicate with the next? The nerve cells interact with each other through so called synapses, which are of two principal types: electrical synapses and chemical synapses. Here, we will focus on the chemical synapses (**slides 17-18)**, which function through chemical signaling between the presynaptic axon and the postsynaptic dendrite (of the next nerve cell). These synapses have a swollen presynaptic knob, in which there are vesicles filled with neurotransmitter molecules. When the electric impulse reaches this synaptic knob, the vesicles move towards the membrane of the knob, where they empty their content into the synaptic cleft. The neurotransmitter molecules then cross the synaptic cleft by diffusion, and bind to a receptor molecule, following the principle of <u>key in lock</u>: one neurotransmitter fits one receptor. (slide **17**)

(slides 19-**20**) What happens in the postsynaptic nerve when the neurotransmitter binds to the receptor molecule? To answer this question we need to describe how a nerve cell at rest function, a nerve cell that does not send any signal: What I mean is that we need to understand the chemical and electrical properties in these cells.

The chemical concentration of the diverse molecules and ions inside and outside a cell will also determine the electrical properties of the cell. The central question is: what is the difference in electrical potential across the cell membrane? This is utmost important since the nerve cell functions by sending electrical impulses, and, when this happens, there is a transient *gross change* in the cell membrane potential, (cf. slide **17**) running the whole way from the cell body, or soma, to the synaptic knob (domino effect), where, as a consequence, neurotransmitters are released as a response to this signal.

A nerve cell at rest (**slide 20**) has a high concentration of potassium ions (K+) inside the cell, and a high concentration of sodium ions (Na+) outside the cell. In any chemical system where there is a concentration difference within a solution (put some colour into a glass of water and watch), or between two compartments separated by a permeable membrane, the substances will diffuse from the compartment of high concentration to the compartment of low concentration. In the nerve cell this results in an outflow of K+ ions and an inflow of Na+ ions.

(**slide 21**) Since the cell membrane is much more permeable to K+ than to Na+, the net flux of K+ out of cell will be much greater than the flux of Na+ into the cell. Since, however, there are multiple huge protein anions inside the cell with a surplus of negative (-) charges on them, molecules which are too large to cross the cell membrane, they will restrict the mobility of the K+ ions: (**next**)

The K+ ions that leave the cell through the K+ channels will therefore ´hang` on the extracellular face of the cell membrane, being dragged there because of the large negative charges on the inner side of the thin membrane. This establishes an electrical potential between inside and outside equal to -70 millivolt (mV), inside negative, outside positive. This is the so called resting membrane potential. (**next**)

The diffusion of ions across the cell membrane would have resulted in a dangerous loss of K+, which concentration has to be constant within the cell, and also an accumulation of Na+ inside the cell, if it had not been for the so called Na+/K+ pump. This energy driven pump

actively transports three Na+ ions out from the cell in exchange for two K+ ions into the cell to re-establish physiological steady state. (**next: slides 24-25**)

Now, if an electrical signal, i.e. a nerve impulse, reaches the nerve end, the synapse, Na + and Ca++ ions will enter the synaptic knob from outside fluid. This will immediately result in a movement of the neurotransmitter-filled vesicles toward the membrane of the synaptic knob. The vesicles fuse with the membrane of the synaptic knob, and empty their content into the synaptic cleft. (**next**)

(**slides:26-29**) Neurotransmitter molecules will now diffuse over the synaptic cleft, and bind to receptor molecules, resulting in influx of Na+ ions into the postsynaptic dendrite: Influx of positive charges will, of course, decrease the potential difference between inside and outside of the dendrite membrane. This potential difference moves down the dendrite (**27-29**) towards the cell body (soma) with some leakage of current out of the cell: let us now say that there is -60mV difference at the so called axon hillock, which is the anatomical site where the axon leaves the cell body.

(**slides: 30-32**) If this is so, nothing will happen. If, however, the potential between inside and outside is reduced to -55mV (the threshold), there will be a change in the membrane properties of the axon[1], leading to a mass influx of Na+, and a total, so called, *depolarization* of the membrane, changing the membrane potential to +40 mV, now with inside positive, and

[1] In the axon membrane there are voltage sensitive channels for sodium, and these will remain close if the membrane potential is more polarized then -55 mV. At -55mV the channel is so unstable that it will allow some influx of Na+. This will lead to further opening of the channel, and, hence, a mass influx of Na+.

outside negative. A nerve impulse is then elicited, and when this happens, the impulse will rush down the axon until the synaptic terminal: a domino effect.

The largest nerve cell axons (slide **35**), such as those following the sensory and the motoric tracts of in the spinal cord, are encapsulated in neuroglia cells, the so called Schwann cells. As remarked previous in this lecture, the neuroglia are wrapped around the fiber constituting a so called myelin sheath, a fat layer, insulating the fiber; that is, it cannot lead electrical current.

Since, however, the Schwann cells are separated by small patches of free cell membrane, the so called nodes of Ranvier, the nerve impulse will be speeded up: What happens is that the nerve impulse jumps[2] from one node of Ranvier to the next, which speeds up the impulse substantially. This is absolute essential for the rapid responses of our muscles, say in a situation where we have to run away from a danger threatening us.

[2] The Na+ ions which enter the axon will "jump" to the next node of Ranvier, depolarizing its membrane, which will lead to an opening of the voltage sensitive Na+ channels in this node, leading to a new mass influx of Na+ ions, and so on, until the synaptic terminal.