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biomax

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Date at our synapses

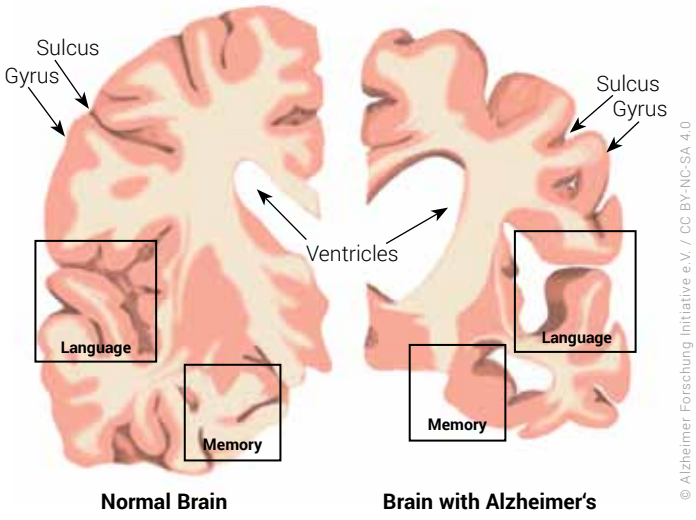
– researchers on the trail of our memories

"What's your name?" - "Auguste." "Your surname?" - "Auguste." - "What's your husband's name?" - "I think it's Auguste." - "Your husband?" – "Oh, my husband..." - "Are you married?" - "To Auguste." - "Mrs Deter?" - "Yes, to Auguste Deter." This conversation between psychiatrist Alois Alzheimer and his patient, Auguste Deter, made medical history. It took place on 25 November 1901, and marked the beginning of research into a disease that remains incurable to this day: Alzheimer's disease. It is regarded as one of the greatest health threats in ageing industrial nations, and an estimated 30 to 35 million people worldwide suffer from this type of dementia.

Auguste Deter was 51 years old when she was admitted to the psychiatric hospital in Frankfurt, and memory loss in such a relatively young woman was a mystery to young Doctor Alois Alzheimer. In December, barely a month later, she could not even remember her own name. When asked "What is your name?", she responded "May," Alzheimer noted. The patient's condition worsened noticeably: she would shout, sometimes for hours, then become completely unresponsive again. She could barely remember any of the details of her life. In one of her rare moments of clarity, Auguste Deter expressed her helplessness succinctly with these words:"I seem to have lost myself." She died of blood poisoning on 8 April 1906. The Director of the institution gave the patient's medical records and brain to Alzheimer, who was then working in Munich at the Royal Psychiatric University Hospital. It was clear even to the naked eye that her brain had a much smaller mass than a normal brain and was deeply furrowed (Fig. A). Six months after Auguste Deters' death, at a psychiatrists' conference in Tübingen in southern Germany, Alzheimer described what he had discovered when viewing the brain slices under a microscope: "I found miliary foci scattered all over the (cerebral) cortex, and very peculiar changes in the neurofibrils." He was describing the two main characteristics of the disease: grainy protein deposits, known as plaques, which are formed when short pieces of a protein called the beta-amyloid peptide clump together, and fibrous protein deposits inside the nerve cells themselves. These are composed chiefly of tau proteins. The usual function of these proteins is to stabilize the cell's microtubules - hollow cylindrical fibres that support the cell's structure. Tau proteins help transport substances from the cell body to the **synapses** - the contact points of the nerve cells. In Alzheimer's disease, they lose their connection to the microtubules and form densely packed protein strands, which then block the nerve cell extensions (axons).

Today's more detailed examination methods reveal that Alzheimer's patients suffer a massive loss of synapses. Some of the billions of nerve-cell circuits storing a lifetime of memories and making up

FIG. A: BRAIN SLICE COMPARISON



the complex personality of a person are lost forever. It's a little like erasing the hard drive on your computer: first, the most recent files are destroyed, then gradually the older data is lost as well. Long before they are even diagnosed with memory loss, Alzheimer's patients have already lost a vast number of synapses. It begins in the areas of the brain responsible for storing memories. This then severely impairs the ability to store new information.

MAKING CONTACT

Neurobiologists have been speculating for more than a century about how memories are stored in the brain. Thanks to the very precise coordination of various genes, nerve cells are linked to each other in very particular patterns during their development; the brain's circuitry is more or less fixed. How can neuron activity affect such a precisely configured set of connections? How do experiences trigger a lasting change in the nerve cells? At the end of the 19th century, the famous Spanish neuroanatomist Ramón y Cajal was one of the first people to realize that changes associated with the storage of information in the brain most probably happen at the contact points between nerve cells - the synapses.

What are synapses, exactly? In the 1950s, when scientists first began looking at the human brain under electron microscopes, they discovered that nerve cells are separated by a narrow gap about 20 nanometres across (a nanometre is a millionth of a millimetre). This is known as the synaptic cleft. Together with this gap, the membrane regions of the two cells on either side of the synaptic cleft - the pre- and post-synaptic What are synapses, exactly? In the 1950s, when scientists first began looking at the human brain under electron microscopes, they discovered that nerve cells are separated by a narrow gap about 20 nanometres across (a nanometre is a millionth of a millimetre). This is known as the synaptic cleft. Together with this gap, the membrane regions of the two cells on either side of the synaptic cleft - the pre- and post-synapticWhat are synapses, exactly? In the 1950s, when scientists first began looking at the human brain under electron microscopes, they discovered that nerve cells are separated by a narrow gap about 20 nanometres across (a nanometre is a millionth of a millimetre). This is known as the synaptic cleft. Together with this gap, the membrane regions of the two cells on either side of the synaptic cleft - the pre- and post-synaptic membranes - form the synapse. The brain of an adult human being contains thousands of trillions of synapses, connecting a total of about a trillion nerve cells. A synapse can have various forms: the fine branches of a nerve cell, known as dendrites (Greek for 'tree'), can form a synapse with other dendrites, axons can form synapses with other axons or even with the cell body of another nerve cell; however, the most common synaptic connection is between an axon and a dendrite.

However, there is now a signal forwarding problem: to communicate with their neighbouring cells, nerve cells generate electrical signals known as **action potentials**. These travel along the entire length of the axon, arriving at the synaptic cleft. This activates the pre-synaptic terminal; the membrane's electrical potential temporarily becomes more positive than when it is at rest (this is called depolarization). But where does this wave of activation go from here? How can it act as a signal to the next receptor cell, if it's stopped by a gap, however tiny that gap may be? It's like driving along in a car and suddenly coming to a river. There's no bridge anywhere in sight. But you can get out of the car and into a boat to cross the river. In the case of nerve cells, that means we need a way to transform the electrical signal into one that cross the synaptic cleft.

When the action potential reaches the pre-synaptic terminal, the membrane depolarization opens channels for calcium ions. The concentration of calcium ions rapidly increases within the synapse. This causes small packages known as **vesicles**, which are loaded with chemical messenger molecules (neurotransmitters), to fuse with the pre-synaptic membrane and release their contents into the synaptic cleft. The more action potentials arrive, the more packages are emptied and the more messenger substance is released. The original electrical signal has now been translated into a chemical one. Within microseconds, the chemical messenger molecules diffuse through the synaptic cleft, crossing it to bind to specific receptors on the surface of the post-synaptic cell. These receptors perfectly match the shape of the arriving molecule, just like a key in a lock. As the messenger substance binds to the receptor, ion channels open on the receiving side. A depolarizing post-synaptic potential builds up - one of the many electrical signals that are transmitted from dendrites to the cell body.

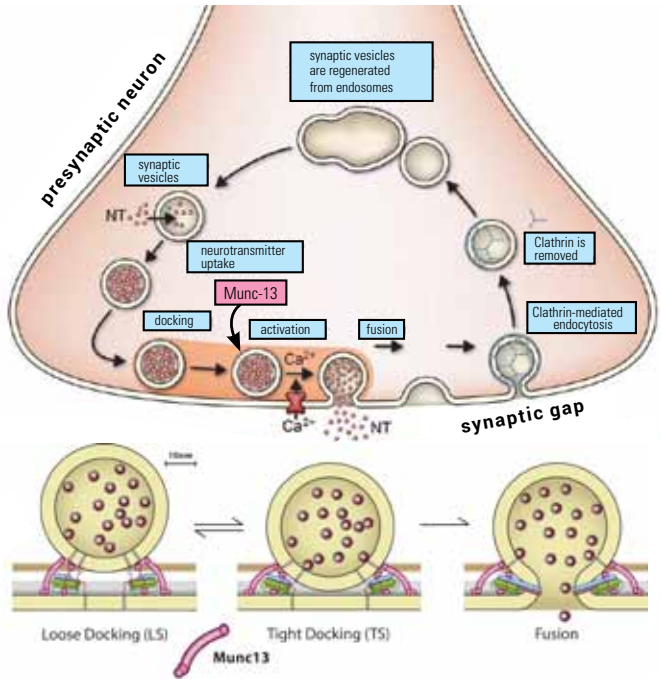
FLEXIBLE PACKAGE DELIVERY SERVICE

This synaptic transmission process can be modified in various ways on the pre-synaptic or the post-synaptic side. This is the advantage of chemical transfer, which is otherwise very time- and energy-consuming. If transmission was limited to just electrical impulses - which also happens within the nervous system - the speed of transmission would be much higher, and there would be no need to produce, store, and then remove the messenger substances. However, by using chemical signal transmission, the transmission strength of the synapse - the efficiency with which an action potential in the transmitting nerve cell activates the receiving cell - can be adjusted. This additional ability to alter

its sensitivity for a certain period of time would be nearly impossible to achieve by simple, passive diffusion of an electrical current from one cell to another. Neurobiologists believe that this **synaptic plasticity** is the basis for many important brain functions, from sound localization and working memory to complex learning processes.

Nils Brose and his team at the Max Planck Institute of Experimental Medicine in Göttingen have spent a long time investigating how synaptic signal transmission is regulated. Some years ago, they discovered a protein known as Munc-13, which not only plays a crucial role in replenishing supplies of vesicles ready for release at synapses, but is also regulated by the activity of nerve cells to ensure the supply of vesicles can be adapted according to need. If there are not enough vesicles available for release, and if they are delivered too slowly, prolonged demand will tire the synapse very quickly. The opposite is true when a synapse is able to rapidly supply fresh fusion-ready vesicles on demand. In some cases, the synapse may even be improved by this prolonged activation. This ability to adapt is called **short-term plasticity**. It enables us to change our behaviour quickly and flexibly in response to input from our senses, or as a result of mental processes, e.g. briefly answering a phone call while working on the computer, locating a honking car in city traffic or catching a ball.

FIG. B: LIFE CYCLE OF A SYNAPTIC VESICLE



The membrane of synaptic vesicles contains a number of proteins that, among other things, ensure the vesicles are able to fuse with the plasma membrane. Munc-13 is one of these proteins. The researchers believe that Munc-13 undergoes a structural change when the vesicle transitions from 'loose docking' to 'tight docking' (see partial image below). After fusion, the vesicles are regenerated within the nerve ending via some intermediate steps, and then refilled with neurotransmitters (NT).

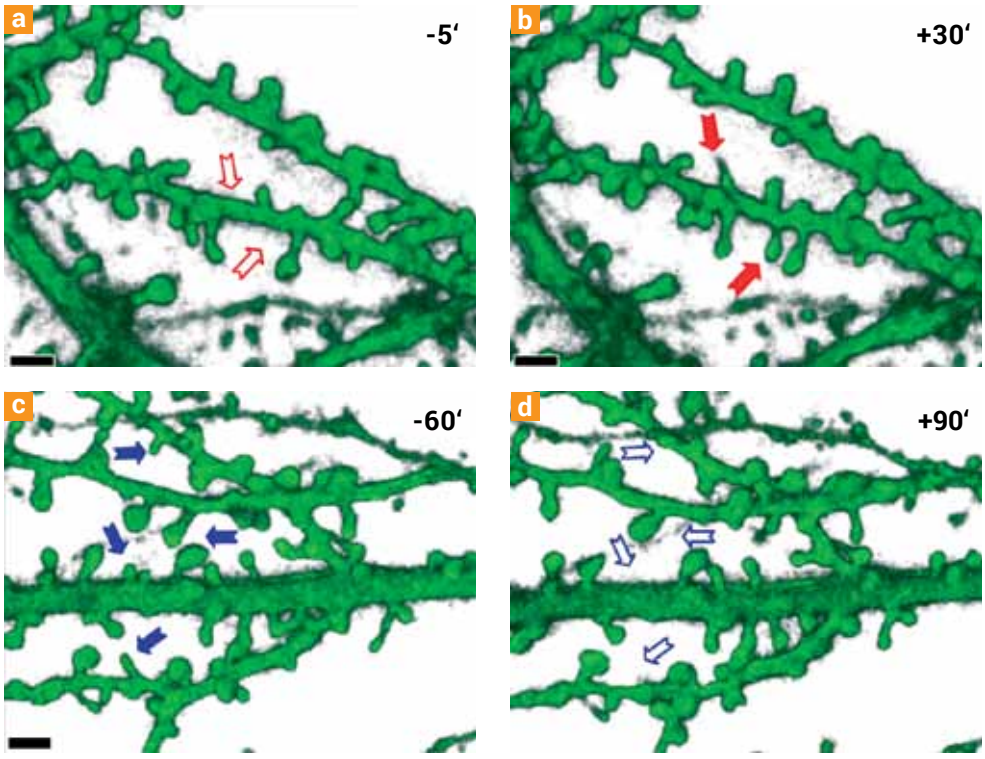
Let's take a closer look at the synaptic vesicles: first they are docked in a specialized area of the plasma membrane called the zone. Before they can fuse with the pre-synaptic membrane, they have to go through a process called priming to mature them ready for fusion. Munc-13 is one of many proteins involved in this process, all working closely together, monitoring each other and ensuring that all the ‚players' are always in the right place. The Göttingen scientists were able to show that fusion-ready synaptic vesicles fluctuate dynamically between two states - called loose docking (8-10nm from the pre-synaptic membrane) and tight docking (2-4nm) **(Fig. B)**. "Electrophysiological experiments show that the transition from loose docking to tight docking is dramatically accelerated by synaptic activity and an increase in the concentration of calcium ions," explains Nils Brose. Since Munc-13 is regulated and activated by calcium ions, it is the ideal candidate for studying the transition between these two vesicle states. The scientists also discovered that if Munc-13 is missing, the synaptic vesicles no longer reach the active zone, but accumulate a few nanometres away.

Based on this data, Brose and his colleagues suggested the following model: two vesicle pools, corresponding to the states of loose docking or tight docking. Vesicles are released chiefly from the 'tight docking pool', as these vesicles have a higher probability of being released. Munc-13 increases the proportion of tightly docked synaptic vesicles at active zone release sites. If this pool of vesicles ready for rapid release is exhausted, it is replenished extremely quickly during synaptic activity. "We think that the speed at which the pool of releasable vesicles is recharged can be explained by the rapid transition of synaptic vesicles from loosely docked to tightly docked," says Brose.

The molecular machinery at the synapse used for various types of learning and short-term storage is extremely versatile. Munc-13 is just one of many examples of how synaptic transmission is regulated. **Short-term memories** are only stored temporarily; retaining them does not require any anatomical change. Switching from a short-term to a long-term memory reinforcement, however, requires switching at a molecular level from a process-based memory to a structure-based one. To enable long-term memory retention, new synapses must be formed. However, this is not so easy to prove. We needed a new technique.

MAKING MEMORIES

Winfried Denk, who now works at the Max Planck Institute of Neurobiology in Martinsried, together with Watt Webb from Cornell University in the USA, had the ground-breaking idea of using two-photon excitation - a concept first described in 1930 by the German physicist Maria Goeppert-Meyer - to construct an extremely powerful microscope. A two-photon microscope can make micrometre-sized structures visible, even those deep inside living tissue. For the first time, neurobiologists were able to literally 'look inside' the living brain and observe how neural circuits change under the influence of experience and learning. In 1999, Tobias Bonhoeffer and his colleagues at the Max Planck



◂ **Fig. C**

Intensive stimulation leads to the formation of dendritic spines on the nerve cells (above), which are marked with fluorescent green protein. Partial image (a) shows a section of nerve cell dendrite before stimulation. After 30 minutes of intensive stimulation, the formation of spines is visible (red arrows - partial image (b)). At a low stimulation frequency, the spines shrink back (below). Partial image (c) shows spines on nerve cells 60 minutes before stimulation. The blue arrows indicate the locations where spines disappear (outlined arrows - partial image (d)).

Institute of Neurobiology in Martinsried were able to use this technique to show for the first time that synaptic enhancement (triggered by intensive stimulation in experiments) actually goes hand-in-hand with tiny anatomical changes **(Fig. C)**: Fine, branching hairs grow into mushroom-like structures consisting of a stem with a head at the end. These are known as dendritic spines. These grow quite purposefully towards possible contact partners. However, these newly-created cell contacts cannot initially exchange any information. Individual dendritic spines vary considerably in whether, and how quickly, a connection is made, and also whether it persists, or whether the spine shrinks back. These contacts, which still persist 24 hours later, have fully functioning synapses, and there is a good chance they will still be there even after several days or weeks have passed.

Conversely, a low stimulation frequency and the resulting weakening of the synapses can lead to the disappearance of these spines. “For the first time, we were able to observe in real time how the brain changes its circuitry during learning,” says Bonhoeffer. Synapses and spines are the brain‘s individual storage units: a single ‘bit’ of storage, so to speak. When something is learned, new connections are created that enhance the contact between two nerve cells. If, on the other hand, the number of synaptic connections is reduced, information is lost and what has been learned is forgotten.

Looking at it like that, the brain is a building site. Our lifelong ability to form new connections and to dissolve them again enables us to perform those mental achievements which make us human. And this is one of the reasons that diseases like Alzheimer’s affect us to our very core. Perhaps one day it might be possible to stop the destruction of synapses caused by Alzheimer‘s disease, without affecting the elimination of synapses that happens naturally during learning and memory. If we could treat patients before they suffer the changes in their ways of thinking and feeling that make it so difficult for them to cope with everyday life, this would significantly improve the quality of life for those affected by this disease. This is why it is so important for researchers to gain a better understanding of the structure of synaptic networks and the reorganization of individual synapses.

Keywords

action potential, Alzheimer’s disease, dementia, short-term memory, short-term plasticity, synapse, synaptic plasticity, vesicle

Links

- *Neuroscience*
  - www.mpg.de/b221 >
  - www.mpg.de/b222
  - www.mpg.de/b223
- *Information about Alzheimer’s Disease*
  - www.mpg.de/b224 >
  - www.mpg.de/b225

Video-Tipps

- *Synaptic Plasticity - How Synapses Fire*
  - www.mpg.de/b226 > youtube
- *Synaptic Plasticity - How the Brain Learns*
  - www.mpg.de/b227 > youtube

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