You can’t teach an old dog new tricks – the old proverb is not totally true. It is now known that the modulation of synaptic functions, including the formation of new neurons, still takes place in old age, although to a lesser extent than in childhood. The human brain stores memories in the form of neural activity patterns. Structural plasticity appears to be the basis for all learning processes. Physician Thomas Hainmüller and Prof. Dr. Marlene Bartos from the Institute of Physiology at the University of Freiburg are investigating mechanisms that are the basis for long-term memory formation and have found that the inhibitory interneurons in the hippocampus play an important role.
Brain neurons communicate with each other through connections known as synapses. Synapses are able to control the strength of the signals transmitted between neurons. Synaptic strength changes according to the number of stimuli received during a learning process: synapses have the ability to weaken or strengthen over time. This phenomenon is called synaptic or functional plasticity and is a natural process that enables organisms to respond appropriately to changes in the environment. Plastic change can also occur due to the quantity of neurotransmitters released into a synapse as well as changes in the number of neurotransmitter receptors located on the post-synaptic membrane. Functional plasticity is therefore the basis of all structural changes in the brain, i.e. it can lead to changes in the size of the synaptic contact area, in the formation of new synapses or in the degradation of synapses that are no longer used.

Thomas Hainmüller is a doctoral student in Prof. Dr. Marlene Bartos’ research group at the University of Freiburg’s Institute of Physiology where he works specifically on the molecular mechanisms of synaptic plasticity. “The adult brain generates new neurons in a few regions only. We therefore believe that learning-related changes occur in the structures that connect individual nerve cells. We currently believe that the major mechanism that enables the formation of memory is somehow related to synapses,” says Hainmüller.

Neuron activity in the brain orchestra

Researchers have only recently found out that new neurons can still be formed in adults in a process called neurogenesis. However, stem cells are only present in two brain regions, the olfactory bulb and the dentate gyrus region of the hippocampus. The hippocampus is generally regarded as the organ where most memories are stored. “There is also convincing evidence that synaptic plasticity is closely linked with the process of learning,” says Hainmüller.

Hainmüller and his colleagues are working on specific types of nerve cells, i.e. excitatory granule cells and inhibitory interneurons. Scientists long believed that the formation of memories in the brain was mainly due to the extremely large number of excitatory neurons. However, it is now known that inhibitory interneurons, of which there are about ten times fewer, also make a significant contribution to our ability to remember things. While excitatory nerve cells activate neighbouring cells, interneurons switch off the following cells, resulting in the separation of similar memories. “Neurons do not act randomly, but synchronously like an orchestra. Specific neurons are active at a specific time; the pause in between is initiated by inhibitory interneurons,” explains Hainmüller, going on to add, “if you switch off the inhibitory interneurons, synchronization is lost.”

I’m being active, and you stay still
Fluorescence microscopy shows how a granule cell (v shape, on the right) is connected to an interneuron (oval, on the left) through a synapse. © Hainmüller/Bartos, University of Freiburg

Nerve cell activity reveals insights into how the strength of synaptic transmission can be modulated. Hainmüller’s work specifically focuses on the synapses of excitatory granule cells, which connect with inhibitory interneurons in the dentate gyrus. “Excitatory granule cells compete with inhibitory interneurons for the information that is transmitted; one granule cell then says to other excitatory granule cells: I’m being active, and you stay still,” says Hainmüller explaining that granule cells give this command using interneurons. “We are trying to find the answers to two questions. First, how can the synapses of these granule cells activate interneurons, which in turn inhibit other granule cells? And second, how does this work during learning and memory formation?”

In order to answer these questions, the character of the synaptic connections and the mechanisms that can change the connections need to be understood in detail. The strengthening of synapses between cells can be achieved if they are all active simultaneously. This basically means that the granule cell must be active at the same time as the interneuron. The latter is then activated more
effectively. The coincident activation of the granule cells and the interneurons is necessary in order to enable the activation of excitatory ionotropic AMPA glutamate receptors and metabotropic glutamate receptors (mGluRs). On the molecular level, plastic change in synapses results from the interaction of several glutamate receptors. The excitatory granule cells release glutamate which binds to fast ionotropic AMPA receptors on the interneuron. Hainmüller and his colleagues have found out that activating the ionotropic AMPA receptors leads to an influx of calcium into the cells. In addition, glutamate excites the slower metabotropic receptors (mGluRs), which in turn trigger a signalling cascade by releasing a G protein into the cell when both granule cell and interneuron are active. “The interplay between calcium and G protein is a prerequisite for plastic change in the post-synaptic cell, which in turn is triggered by a second-messenger cascade,” says Hainmüller.

Plasticity separates memories

Long-term plasticity forms memories: The interneuronal protein kinase C (PKC) sends a signal back to the granule cell, which then gives priority to this connection, resulting in the release of larger quantities of neurotransmitter. © Hainmüller/Bartos, modified from PNAS: Joint CP-AMPA and group I mGlu receptor activation is required for synaptic plasticity in dentate gyrus fast-spiking interneurons (2014; 111: 13211-6)
occurs upon the coincident activation of granule cells and interneurons. This, and only this, leads to a tighter connection between the two, and enables the granule cells to activate the interneurons to a greater extent. The researchers have also observed that this promotes the silencing of less active neurons. “This might enable the further separation of two different pieces of information by preventing an overlap and reducing the cells’ activity level,” says Hainmüller comparing it to a traffic light where red and green lights have to be clearly separated. Long-term synaptic plasticity is induced by the interneural protein kinase C (PKC) enzyme that sends a retrograde signal (the nature of which is as yet unknown) to the pre-synapse, thus increasing the probability of the granule cell releasing neurotransmitters over a long duration (long-term plasticity).

Bartos’ team has been able to show in mice that switching off the animals’ interneurons prevents them from forming memory during the period the interneurons are switched off. The animals reveal deficits in their working memory. On the other hand, recent studies have shown that it is possible to generate artificial synaptic plasticity using optogenetics, which results in the memorization of new information. However, Hainmüller is cautious about any potential medical application of the findings for the treatment of dementia and memory disorders. “We first need to obtain a detailed understanding about how the brain learns. When we know this, we will then be able to think about ways to correct deviations.”

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