New insights into the molecular basis of memory

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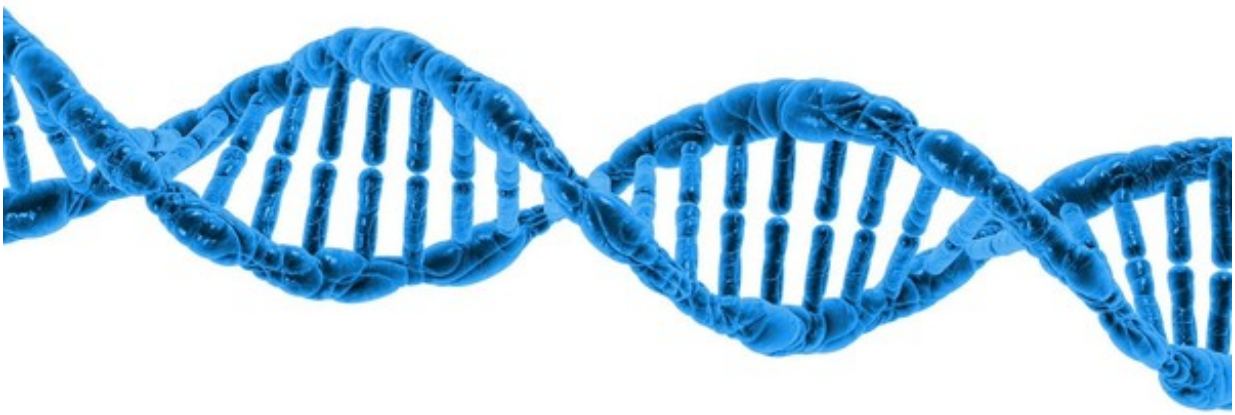

Scientists from the German Center for Neurodegenerative Diseases have shed new light on the molecular basis of memory. Their study confirms that the formation of memories is accompanied by an altered activity of specific genes. In addition, they found an unprecedented amount of evidence that supports the hypothesis that chemical labels on the backbone of the DNA (so-called DNA methylation) may be the

molecular basis of long-term memory. These findings are reported in *Nature Neuroscience*.

The brain still harbours many unknowns. Basically, it is believed that it stores experiences by altering the connections between brain cells. This ability to adapt—which is also called "plasticity"—provides the basis for memory and learning, which is the ability to draw conclusions from memories. On a molecular scale, these changes are mediated by modifications of expression of specific genes that strengthen or weaken the connections between the brain cells as required.

In the current study, a research team led by Dr. Stefan Bonn and Prof. André Fischer from Göttingen, joined forces with colleagues from the DZNE's Munich site to examine how the activity of such genes is regulated. The scientists stimulated long-term memory in mice by training the animals to recognise a specific test environment. Based on tissue samples, the researchers could discern the extent to which this learning task triggered changes in the activity of the genes in the mice's brain cells. Their focus was directed on so-called epigenetic modifications. These modifications involve the DNA and DNA-associated proteins.

Epigenetic modifications

"The cell makes use of various mechanisms in order to turn genes on or off, without altering the DNA sequence itself. It's called 'epigenetics'," explains Dr. Magali Hennion, a staff member of the research group of Stefan Bonn.

In principle, gene regulation can happen through methylation, whereby the backbone of the DNA is chemically labeled at specific sites. Changes in the proteins called histones that are packaging the DNA may also occur.

Hennion: "Research on epigenetic changes that are related to memory processes is still at an early stage. We look at such features not only for the purpose of a better understanding of how memory works—we also look for potential targets for drugs that may counteract memory decline. Ultimately, our research is about therapies against Alzheimer's and similar brain diseases."

A code for memory contents?

In the current study, the researchers found modifications, both of the histones as well as of the methylation of the DNA. However, histone modifications had little effect on the activity of genes involved in neuroplasticity. Furthermore, Bonn and his colleagues not only discovered epigenetic modifications in nerve cells, but also in non-neuronal cells of the brain.

"The relevance of non-neuronal cells for memory is an interesting topic that we will continue to pursue," says André Fischer, site speaker for the DZNE in Göttingen and professor at the University Medical Center Göttingen (UMG). "Furthermore, our observations suggest that neuroplasticity is, to a large extent, regulated by DNA methylation. Although this is not a new hypothesis, our study provides an unprecedented amount of supporting evidence for this. Thus, methylation may indeed be an important molecular constituent of long-term memory. In such a case, methylation could be a sort of code for memory content and a potential target for therapies against Alzheimer's disease. This is an aspect that we specifically want to focus on, in further studies."

More information: Rashi Halder et al. DNA methylation changes in plasticity genes accompany the formation and maintenance of memory, *Nature Neuroscience* (2015). DOI: 10.1038/nn.4194

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