Impaired Contact in Neuronal Networks

Some symptoms of autism and schizophrenia are similar: those affected show signs of disturbances in social behavior, become withdrawn and tend toward stereotypes.

So it comes as no surprise that the participants at the second symposium of the Göttingen Research Association for Schizophrenia also discussed the topic of autism in great detail—in the hope that the first genetic animal model for autism might also be used to obtain findings relating to the other disease pattern. Yet even without fully understanding schizophrenia, medical experts have been successfully testing new drugs: EPO, for example, which has already been helping cyclists reach new heights.

According to Nils Brose, Director at the Max Planck Institute of Experimental Medicine in Göttingen, it took his team 13 years of work—13 years in which, at least, the researchers didn’t have to fear being surpassed by the competition.

“Our colleagues thought it was far too tedious,” says Brose. “But with a predisposition for a form of autism, “In this way, we created the first genetic animal model for autism,” the biochemist explained recently at the Second International Symposium on Schizophrenia of the Göttingen Research Association for Schizophrenia.

Such animal models are considered to be an important prerequisite for better understanding illnesses. The fact that a schizophrenia conference devoted so much of its time to autism might seem odd at first. But with previous animal models, we’d just been groping in the dark,” says Ehrenreich. More than 60 years after American psychiatrist Leo Kanner discovered what we assume happens in the brains of autists.

Autistic mice lack several variants of the so-called neuregulin genes. These carry the blueprints for proteins that play an important role in proper communication between neurons. The neurons are connected with each other via the synapses. At these points of contact, they emit neurotransmitters, chemical messengers that cross a tiny gap to reach the next neuron. If one twin develops the disorder, the risk of the other becoming ill is around 90 percent.

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The study, the number of new cases of autism is identified by the University of Texas. According to the US about a study conducted by several. For example, there is a heat-wave effect on the number of cases but remains unclear – there are probably several. Some experts are still skeptical about the trend, but the CDC verified its data several times. So, added to a genetic basis, certain environmental influences ought to play a role, says Herbert.

Which factors could be involved remains unclear – there are probably several. For example, there is a heated debate among medical experts in the US about a study conducted by the University of Texas. According to the study, the number of new cases of autism increased dramatically in an area of Texas with high levels of mercury pollution. In certain rural schools, the number of cases climbed more than 60 percent. Despite this, Herbert warned against scaremongering, as the data is still preliminary and must be validated in larger studies. And in any case, many other environmental factors could be involved, even in the womb before birth – food, drugs, stress hormones and various other things could harm the fetus.

However, anatomical changes have been clearly proven: as different teams of researchers have discovered, the brains of many autistic children grow at above-average levels in the first years of life. “This is a new finding in medicine,” explained Martha Herbert, a physician. In Göttingen, she summarized the results of the various projects. The children actually appear to be born with brains of below-average size, as shown by simple measurements of the circumference of their heads. Then, between the first and second months after birth, the brains of autists grow rapidly, and then again from the sixth month after birth until two years of age.

**FeWER NeURONS, More Cables**

Up until five years of age, the speed of growth gradually slows down. At this point, however, the brain of an autist is already as big as that of a healthy 13-year-old. In contrast, the size of an autistic brain does not appear to increase any further during adolescence. “It’s striking that the brain doesn’t change until after birth,” Herbert points out. Particularly the frontal lobes of the cerebral cortex – which are responsible for our social behavior, among other things – seem to grow excessively in early childhood. In contrast, the neurons themselves, represented anatomically in the so-called gray matter, are smaller than usual. Growth occurs almost exclusively in the white matter. This consists of axons, the cables that convey arousal and connect the neurons in different regions of the brain. Martha Herbert was able to prove that particularly the white matter in the right cerebral hemisphere gains in size. Neighboring areas of the brain appear to have an unusually large number of connections, while there are only a few connections to more distant areas, as well as between the two hemispheres.

“The networking between different areas of the brain doesn’t work properly,” Herbert said at the symposium.

No one knows yet what the changes mean. Above all, are the networking problems a result of autism, or its cause? The abnormal growth of the brain may even have something to do with the immune system. US researchers found some indication that the brains of autists are chronically inflamed throughout their entire lives. This is suggested by an elevated number of a certain type of immune cells in the brain. While such findings have not yet brought about any advances in therapy, Hannsloren Ehrenreich presented a new treatment study of schizophrenic patients. Around 800,000 German citizens develop a schizophrenic disorder at least once in their lives, usually for the first time between the ages of 18 and 35. Men and women are equally likely to be affected, and most are able to work at least occasionally despite the disorder. Patients believe, for example, that their thoughts and feelings are controlled by an external force – they hear voices commenting on their actions or giving orders; they suffer delusions, for example about being able to control the weather; they suddenly lose their train of thought.

Docteurs characterize all of these disorders as positive symptoms that can treat with antipsychotic drugs – as opposed to the negative symptoms and cognitive changes that occur in two-thirds of all patients: affective flattening and dwingling ability to experience pleasure, lasting personality changes, lack of initiative, social withdrawal and decreased ability to socialize. “Erythromelain,” Ehrenreich emphasizes, “is the very first drug that improves the cognitive impairment.” The drug, called EPO for short, is a notorious psychotic drug as their basic medication and who exhibited similarities in the progression of the disorder and in psychopathological traits. They were divided into two groups, the test subjects in one group receiving a high dose of EPO once a week for three months, and the other’s a placebo.

For two years, Ehrenreich and her colleagues monitored a total of 39 patients. “The patients who received
treatment,” explains Ehrenreich, “demonstrated significantly improved cognitive performance – for example with regard to attention span and memory, as well as executive functions, which people use to plan and structure their actions.”

Medical experts have not yet noticed any adverse effects. “EPO can regenerate the brain to a certain extent,” says the Göttingen-based Max Planck researcher. However, her team was more than a little surprised by the unexpectedly large placebo effect within the control group. The reasons for this are obvious. Schizophrenia patients often live in isolation, far removed from society. “In a study,” says Hannelore Ehrenreich, “they’re suddenly important; they feel noticed.” That alone can change their lives, and their cognitive functioning along with it. In two follow-up studies, the scientists want to test the effect of administering EPO for a longer period, and to shed further light on the placebo effect.

GABA ALONE DOESN’T HELP

EPO did not, however, relieve the patients’ positive symptoms that respond to antipsychotic medication. Nevertheless, the traditional principles of drug development and effects do not seem to apply to the interneuron GABA system, since researchers were unable to relieve the symptoms of schizophrenia by activating the neurotransmitter’s signaling system. For this reason, medical experts are searching for certain subtypes of GABA receptors that promise some effect. As Hannelore Ehrenreich points out, perhaps the entire GABA system ought to be modulated instead – for example with growth factors or other substances that increase the sensitivity of the entire system and thereby normalize it. “But we’re still very much at the beginning,” says Ehrenreich. And this is where the animal models come into play again. Klaus-Armin Nave, also of the Max Planck Institute of Experimental Medicine, blocked the neuregulin-1 gene in mice in certain neurons and at certain times. This is one of the estimated 50 genes in which an error entails a risk of schizophrenia. Neuregulin-1 ensures, among other things, that the neuronal processes acquire their important myelin sheath. To Nave’s surprise, however, the knockout mice showed no symptoms of schizophrenia. So was the experiment a failure? Not at all, thought some of the participants at the symposium in Göttingen. Now the rodents with a genetic predisposition for a form of schizophrenia, but with an apparently normal brain configuration, can be confronted with certain environmental factors that could be important for the development of the disorder. After all, the risk of acquiring the disorder is only 50 percent genetic. The remaining 50 percent must have to do with the patients’ life stories – stress, drug abuse, psychological traumas. “Using combined animal models such as these,” notes Hannelore Ehrenreich, “we are getting closer to the roots of schizophrenia.”

KLAUS WILHELM

On the evening before the symposium, there was an event on “Schizophrenia and Art” with Klaus-Armin Nave, Rosa Reichenbach, Hannelore Ehrenreich, Eduard Beaucamp and Thomas Riske (from left). The panel discussion on the following day was devoted to the topic “Schizophrenia – Loss of Inhibition?” (right).