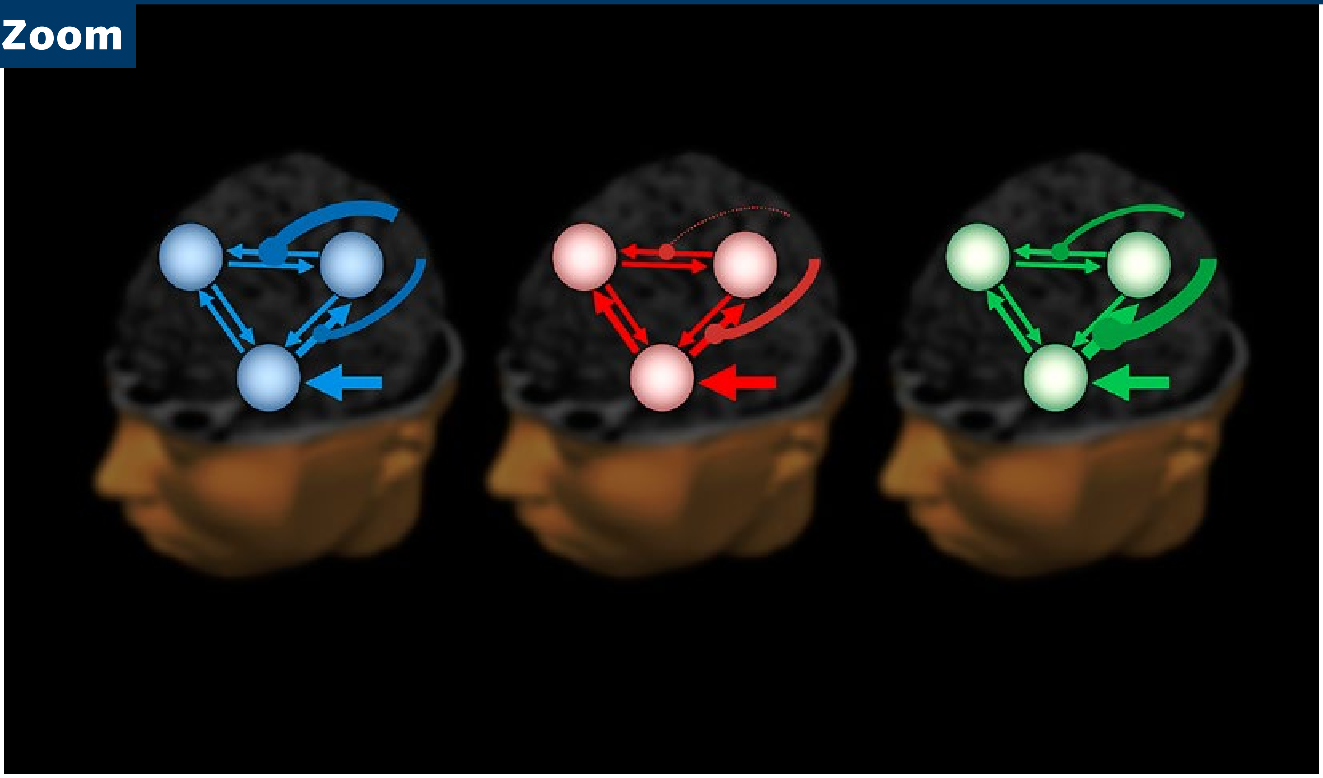

Using functional magnetic resonance imaging, a mathematical model can help researchers to draw conclusions about the degree to which schizophrenia patients are afflicted.

Translational Neuromodeling Unit

New paths for psychiatry

Maja Schaffner

Klaas Enno Stephan and his group develop mathematical models to examine psychiatric illnesses. Their long-term goal is to find tests for psychiatry permitting rapid, accurate diagnoses so as to give patients individual, targeted treatment.

"Today, patients with psychiatric disorders are more or less treated according to the 'trial and error' principle", says Klaas Enno Stephan, Professor at the Institute of Biomedical Engineering. The reason is that standardised questionnaires are in most cases the only tool available to identify psychiatric complaints. Diagnoses can be based on the symptoms but it is not possible to identify the mechanisms behind the condition. This is in contrast to physical disorders where, for instance, blood tests can help to clarify the underlying causes. It can thus take several months to find an effective drug treatment for psychiatric disorders. "This is very distressing for the patients who often have to accept what may be major side-effects without knowing whether a specific drug can really help", says Stephan.

This is where Stephan's research group comes in – the Translational Neuromodeling Unit. It develops novel tests intended to lead to rapid, accurate diagnoses which in future will enable psychiatric disorders to be treated appropriately from the very beginning.

The tests are based on mathematical models used to analyse images of the active brain. "The models are always simplifications of the actual hidden processes in the brain", explains Stephan. "However, they do render changes in brain activity visible and allow conclusions to be drawn about the causes of a psychiatric disorder."

Diagnosing schizophrenia

The scientists recently demonstrated that these models work for schizophrenia patients. They succeeded in distinguishing between test persons with and without schizophrenia, and also divided them into subgroups.

This "simple mathematical model" (thus Stephan) makes such differentiation possible by analysing brain activity by means of functional magnetic resonance imaging (fMRI) and presenting the results as an image. From these measurements the model calculates the strength of coupling, i.e. the intensity of communication among three selected brain regions. These coupling strengths permit conclusions about the type and severity of the disease afflicting schizophrenia patients.

In practice, the researchers tested their model by asking patients with schizophrenia and a control group of healthy test persons to look at images and remember them. During this working-memory task they recorded the participants' brain activity. This revealed major differences between the coupling strengths of the three brain regions of the control persons and patients.

Furthermore, with the help of their model the researchers were able to divide the schizophrenia patients into three groups with different patterns in coupling strengths. When these results were compared with their clinical symptoms, everyone was surprised to find that the three groups indeed represented varying degrees of severity of schizophrenia.

Further studies will be needed before the current model can be implemented in practice. "What we particularly lack are tests with patients who at the time of the study had not yet taken any medication. If researchers had access to such patients, they could observe over time how the disease develops, which medicines help and whether the model's predictions concerning the disease's trajectory actually prove to be true", says Stephan.

On the trail of neurotransmitters

Another mathematical model on which the researchers are working looks at neurotransmitters, i.e. the messenger substances in the brain like dopamine or acetylcholine. An imbalance in these messenger substances is one of the most frequent causes of psychiatric disease – too much or too little can have disastrous consequences. The problem is that today's methods mean it is impossible to determine clearly which of the messenger substances triggers a specific symptom in a patient. Understanding this would, however, be the key to targeted treatment.

The researchers' model visualises the activity in the brain regions which are of relevance for the formation of specific neurotransmitters. The scientists showed that this model works, too, by asking the test persons to solve learning tasks on the computer. They were asked to predict specific images. Using a model, the brain activity recorded using fMRI let them determine how and where these learning processes take place in the brain. They took a closer look at specific areas of the brain which are involved in the production of messenger substances.

Stephan's team is the first research group to succeed in accurately measuring activity in the basal frontal lobes of the brain where the messenger substance acetylcholine is formed. This had not been achieved up to now without mathematical modelling. In the midbrain, too, where dopamine is produced, the researchers were able to take reliable measurements using the model.

Both messenger substances have extremely important effects on the brain and, when disrupted, trigger severe illness. Acetylcholine plays a key role, for instance, in Alzheimer's disease. In Parkinson patients, dopamine-forming neurons die off. Dopamine is also involved in psychiatric diseases like schizophrenia, compulsive disorders or depression.

"Our models supply promising indicators for the work of these neurotransmitters", says Stephan. The researchers would like to continue testing their results in patient studies. If these are successful, they would fine-tune tests for practical use.

"By taking measurements at the start of treatment, we will hopefully be able to use these tests someday to predict how well someone will respond to a drug and the dose he should be given", explains Stephan. ■

First institution of its kind

The Translational Neuromodeling Unit (TNU) is a joint institution of the University of Zurich and ETH Zurich and is attached to the Institute of Biomedical Engineering. Thanks to the cooperation between the two universities and a donation from the René and Susanne Braginsky Foundation, it was set up very quickly with minimum red tape in 2012.

At the TNU, which is headed by Klaas Enno Stephan, IT experts, electrical engineers and physicists work together with biologists, psychologists, doctors and medical staff. Stephan himself is a doctor and neuroinformatics scientist. The researchers have their own outpatient research unit at their disposal.

The distinguishing feature of TNU is that the scientists not only develop and test the models but they also want to fine-tune them themselves into tests that can be used in psychiatry. Up to now, this is a truly unique combination on the global stage.

www.translationalneuromodeling.org →