

Healthcare industry BW

Parkinson's disease – a fatal cycle of falling and rising activity in the basal ganglia

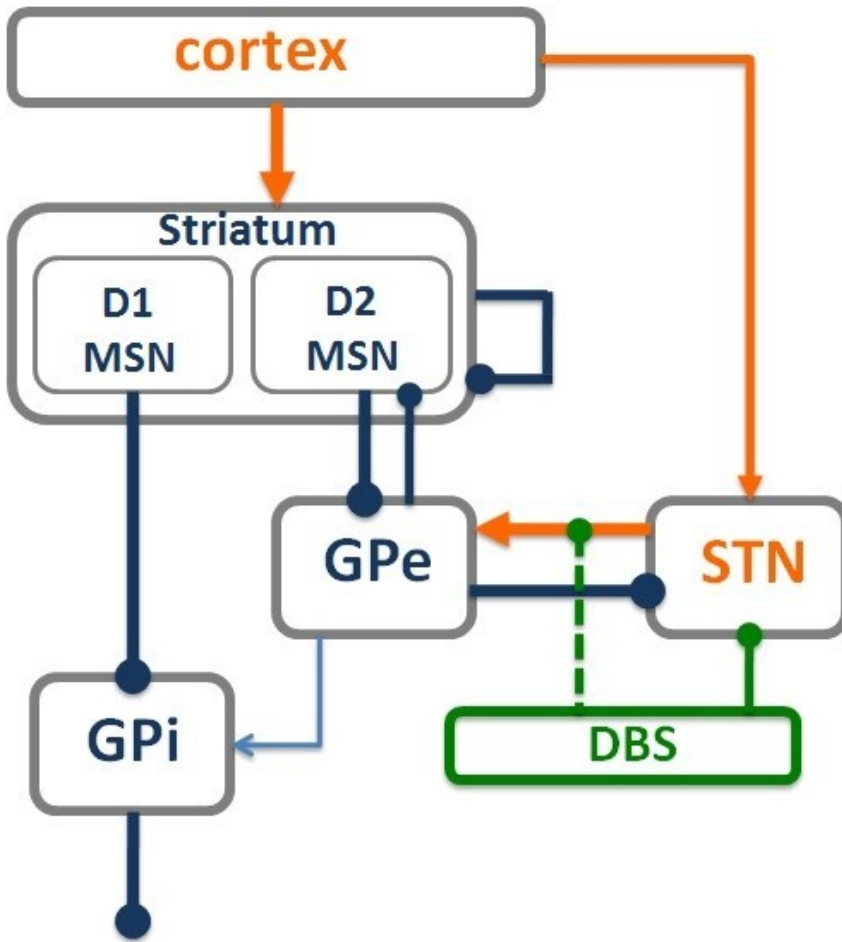
As the disease progresses, Parkinson's patients find it increasingly difficult to voluntarily control body movements. The disease is associated with oscillations of electrical activity in specific brain areas known as basal ganglia. Dr. Arvind Kumar and his colleagues at the Bernstein Center Freiburg have used neuronal network simulations to develop a model to explain these rhythmic oscillations. Do other brain areas also contribute to Parkinson's disease symptoms? Can the new model be used to optimise the treatment of Parkinson's disease; how can deep brain stimulation counteract Parkinson's symptoms and how can the method be improved? Can movements in Parkinson's patients be voluntarily controlled by willpower? Kumar and his colleagues are focusing specifically on the interaction between different brain areas.

In Parkinson's, a group of nuclei known as basal ganglia that are located at the base of the forebrain and connected with the cerebral cortex somehow end up out of balance. Researchers believe that this is why Parkinson's patients gradually lose the ability to control their movements. The disease is characterised by the depletion of dopamine due to the degeneration of dopamine-producing cells in the substantia nigra brain area. This leads to sudden oscillations in electrical activity – a periodic rise and fall in activity – which causes jerks and twitches; sufferers lose control of their movement apparatus. A method known as deep brain stimulation (DBS) can be used to reduce motor symptoms. DBS is a surgical treatment involving the implantation of a pacemaker into the brain, which sends electrical impulses to specific parts of the brain by way of electrodes, thereby changing brain activity in a controlled manner and quenching the oscillations and suppressing disease symptoms. "But why do such oscillations in the basal ganglia appear?" asks Dr. Arvind Kumar from the Bernstein Center Freiburg (BCF). "How can deep brain stimulation act against such oscillations?" The researchers compare the basal ganglia to a box that emits disturbing noise; they have worked out how to shake the box in a way that silences the noise, but do not yet know in detail how the noise is generated.

Proposing a new model

Until recently it was thought that the oscillations occur in response to changing signals in the basal ganglia. This assumption is based on the fact that two particular nuclei in the basal ganglia - the globus pallidus externus and the subthalamic nucleus - are connected with each other by a loop of excitatory and inhibitory pathways: when the strength of the inhibitory signal diminishes,

Simplified network model of the basal ganglia



Simplified network model of the basal ganglia, a brain area that plays a crucial role in the development of Parkinson's disease: GP= globus pallidus; STN= subthalamic nucleus; DBS= deep brain stimulation
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the excitatory input gets the upper hand. This leads to the activation of the inhibitory pathway, more inhibitory signals are sent; this then quenches the excitatory activity, which in turns leads to a rise in inhibitory activity, and so it goes on - a cycle of rising and falling activity. "This model is quite smart," said Kumar adding "but it is not in line with the latest experimental findings." The researchers have found out that the strengths of the connections between the two nuclei of the basal ganglia do not alter at all in Parkinson's patients. Instead they found that the excessive activity of the striatum forces the basal ganglia into oscillations. The striatum is connected with the thalamus, receives input from the cerebral cortex as well as being the major input station of the basal ganglia system.

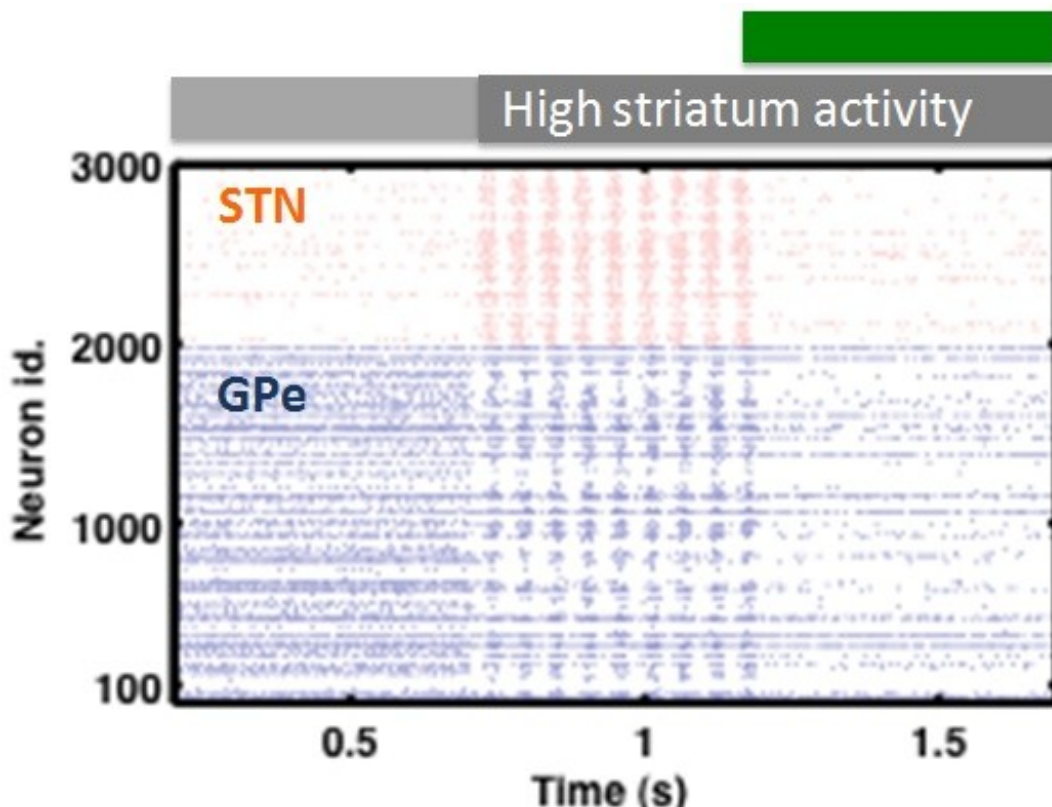
Kumar and his colleagues from the BCF have recently proposed a new model in which the input from the striatum rather than the connections between the nuclei of the basal ganglia alter. The researchers simulated the system of inhibitory and excitatory loops using a realistic network model consisting of 3,000 neurons. They either quenched the inhibitory activity in the globus pallidus externus or stimulated the excitatory subthalamic nucleus and they found that the oscillations in electrical activity that are typical for Parkinson's occurred. "Our experiments showed that the oscillations in activity in the basal ganglia occurred as a result of the altered input from the

striatum,” said Kumar. So the question arises as to whether deep brain stimulation, as a method that is able to compensate the altered input from the striatum, can counteract such oscillations. In order to answer this question, the researchers from Freiburg simulated the effect of deep brain stimulation on the input signals from the striatum and succeeded in warding off the oscillations. In addition, they also successfully developed an optimised stimulation protocol that only uses half the pulses currently in use for DBS. This could double the battery life span of the DBS implant and hence reduce the number of battery replacement operations.

Theory and clinical application

“Using our model we are finally able to satisfactorily explain the occurrence of oscillations that are typical of Parkinson’s,” said Kumar. “And there’s more: the model also shows why the control of movements by willpower is difficult to achieve in Parkinson’s patients.” Kumar and his colleagues know from other experiments that the input from the striatum is crucial for the voluntary control of certain movements. If a volunteer wants to suppress a movement, the striatum stimulates the inhibitory activity in the globus pallidus which then sends out a no-go signal. This results in a two-second oscillation of the activity in the basal ganglia, which makes movement impossible. Parkinson’s patients are in a permanent “no-go state”: movements are initiated over and over again, but immediately blocked.

Kumar and his colleagues from Freiburg are currently analysing electrophysiological data from Parkinson’s patients and are planning clinical experiments to validate their model in real human brains. They are also simultaneously working on other projects; in one, they have recently shown how the connections between the striatum and the cortex are organised. One still unanswered question focuses on why the activity of the striatum alters in Parkinson’s patients and whether higher brain centres also have an effect on the motor symptoms. It is assumed that the voluntary control of movement occurs in the cerebral cortex. What role does the cortex play in the generation of erroneous activity that builds up to oscillations in the basal ganglia of Parkinson’s patients?



Origin of oscillations in PD & their quenching after DBS

Low activity in the striatum quenches oscillations and high activity unleashes oscillations (in the photo the activity increases after 0.75 seconds). The deep brain stimulation simulated in the model (green bar) is able to quench the activity and hence prevent oscillations in Parkinson's. GP = globus pallidus; STN = subthalamic nucleus.

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Kumar is also investigating the interactions between different centres of the visual system. He is working on basic questions relating to the integration of individual neurons in a large network: which network partners does a neuron need to be in contact with in order to have the maximum effect possible on the network? And which cells have little effect despite high levels of activity? There is a lot of theoretical work that requires mathematical models. This work – as the Parkinson's project clearly shows – is important for basic research as well as clinical application.

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