Controlling the brain

People with brain disorders like Parkinson's disease and tinnitus may one day have an ingenious, miniaturised neurosimulator implanted in their bodies. Made in Delft.

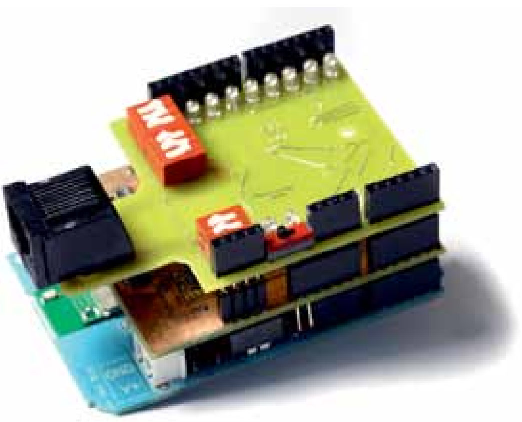
The Parkinson's patient presses a button on his remote control, and suddenly his violent spasms cease. The man has just activated his neurotransmitter, a device the size of a mobile phone implanted in his chest. It sends electrical impulses via a cable to electrodes in certain areas of the brain which exhibit abnormal activity. The neurostimulator suppresses these brain regions.
"It's fantastic to see how well the technique works for this patient," says electrical engineer Marijn van Dongen, as he shows a film of this seemingly miraculous cure on his computer. "Electrical currents flowing around our bodies determine a good deal of how we function," continues the PhD student in the Micro-electronics department of the faculty of Electrical Engineering, Mathematics and Computer Science (EEMCS). "Intervening in that process allows us to tackle numerous brain disorders, like Parkinsonism, tinnitus or epileptic attacks, on a highly localised basis."
"However", Van Dongen adds after a brief pause, "at the same time these techniques are really rather medieval."

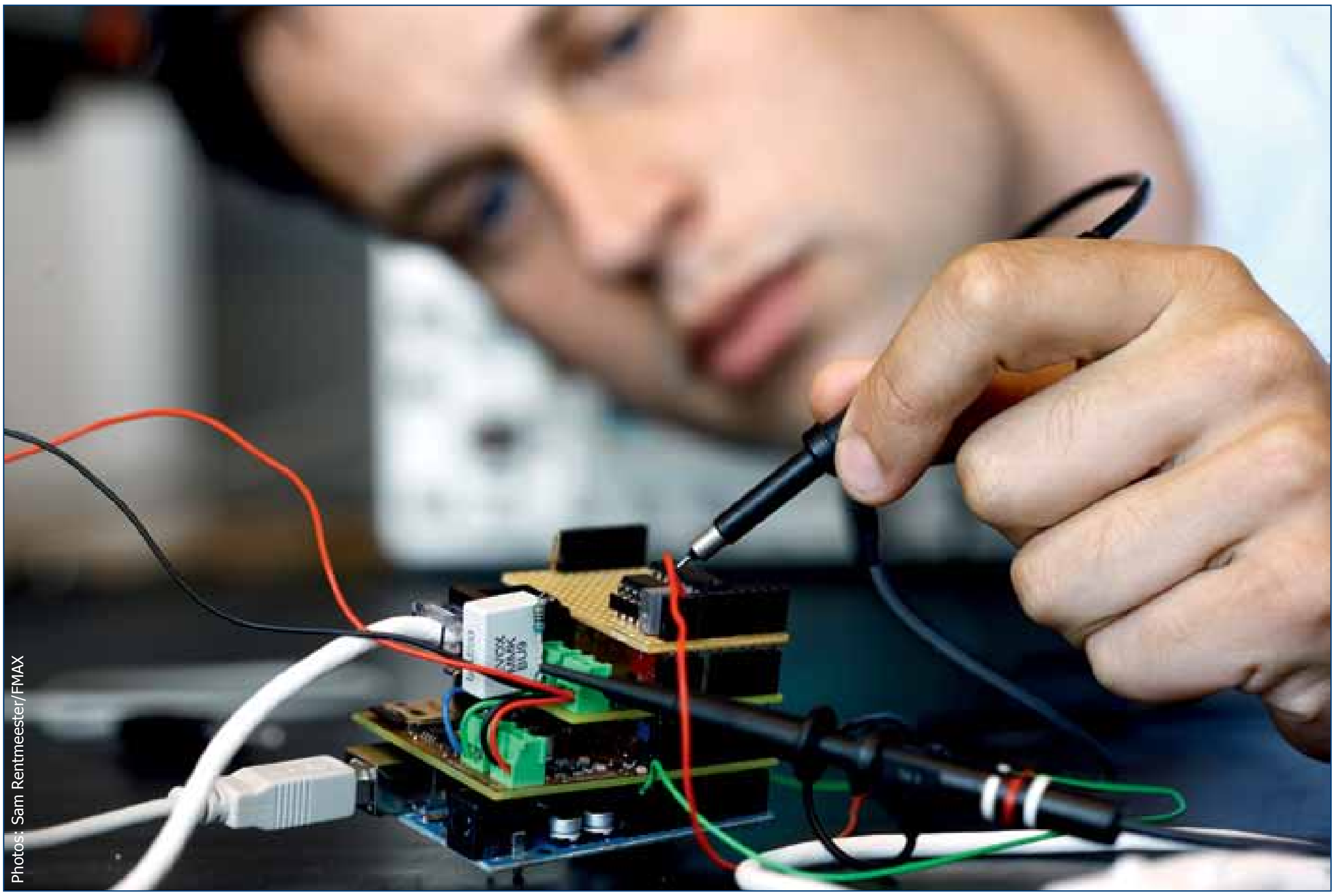
'The great challenge is to get the neurostimulator to listen to the cacophony in the brain'

The electrical cables that run up the neck and into the brain can break or cause infections; they also cause scar tissue in the neck, making it painful for patients to move their heads.
But these tribulations aren't really what Van Dongen is referring to. It's the design of the stimulator he thinks is "medieval". The present design is impeding further miniaturisation, so the entire design needs to be revised to get around the business with the cables.
Van Dongen and various colleagues in the Smart Implantable Neurostimulators (Sins) research programme are working on a completely new design for the implant. Their goal is to have a neurostimulator - a 2mm thick by 2cm square device also housing the battery and antenna - ready for implantation inside the cranium within ten years.
The research programme was launched in 2008 when neurosurgeon, Professor Dirk De Ridder, and neuroscientist, Eddy van der Velden, from University Hospital in Antwerp, Belgium, met up with Dr Wouter Serdijn (Micro-electronics department - EEMCS). Serdijn specialises in the design of electronic circuits for medical implants.
The two neuroscientists, who work primarily with tinnitus sufferers, asked Serdijn if he could make smaller, smarter stimulators for them. "These new stimulators will also need to be able to detect when they should generate impulses by analysing the signals from the brain, just like a pacemaker does with the heart", says Serdijn, the TU Delft programme manager for Sins.
The impulse patterns must be adjustable, and more natural in form - not angular as they are now. The current impulses look like the crenellations on a castle wall. This is so unnatural for the brain that the neurostimulator often fails to effectively suppress or control the relevant brain region. This means that the technique doesn't work for half of all tinnitus patients.

Sardines

Van Dongen has a neurostimulator lying on his desk, the same type of device as the man in the film has in his body. The upper section of the titanium frame has been peeled back like a tin of sardines. "Just look at it," he sighs. "A massive battery, loads of separate components on a circuit board, large condensers."
Van Dongen wants to integrate all the separate components into a chip, and get rid





Marijn van Dongen:"The new design allows us to give the pulses any form we like"

of the space-consuming condensers.
The condensers ensure that the positive and negative currents are balanced, which is not a minor matter: all electrons sent into the tissue need to flow back later, otherwise all kinds of electrolytic reactions will occur around the electrodes in the brain.
In the new design made by TU Delft scientists, the condensers are replaced by electronic circuits that monitor the currents flowing in and out of the brain.
The researchers have already completed a prototype of the equipment which will eventually be implanted in the brain. It is still a little larger than the existing stimulators, but it will be miniaturised in the coming years.
The TU Delft researchers recently tested the prototype. "This was a first test, intended to see if our neurostimulator is able to produce anything like a suitable neural response," says Van Dongen. The test was successful.
Neuroscientists De Ridder and Van der Velden acted as test subjects, with each having electrodes temporarily implanted in their brains. They were able to control the stimulator via an iPhone app. The scientists then used electroencephalography to measure the responses.
The great challenge is to get the neurostimulator to listen to the cacophony in the brain and then respond very precisely with stronger or weaker impulses according to need, just as a pacemaker does with the heart. The researchers refer to this as a "closed loop". With a pacemaker, the task is relatively simple. That device only needs to monitor a single wave - the beating of the heart. The electrodes in the brain by contrast must deal with thousands of neurons.
The medical researchers are hoping that the closed loop technique will allow for a better understanding of the brain and any irregularities occurring within it, which will allow for improved therapies to be developed.
"So we are working on sensor electronics that can zoom in on the specific frequency bands where the problems occur," says Senad Hiseni, another PhD student working in Serdijn's group. "This would have several advantages. Take tinnitus, for example, twhich is caused by unusual activity in the auditory cortex, the region of the brain where sound is perceived. Tinnitus doesn't always occur at the same spot, and the source can even change location. A closed loop system allows the stimulator to keep track of that change and only provide stimulation where it is needed. Tinnitus can be more efficiently countered, and the energy requirement is lower, extending battery life."

'Electrical currents in our bodies determine a good deal of how we function'

The new design is still a long way from being a closed loop, and it isn't very small yet, either. But it is already flexible. "The new design allows us to give the pulses any form we like," Van Dongen says. "The circuitry takes care of balancing the load. So we are no longer tied to angular impulses. We could even fire Rolling Stones music at the brain." Serdijn laughs: "But maybe AC/DC would be better."

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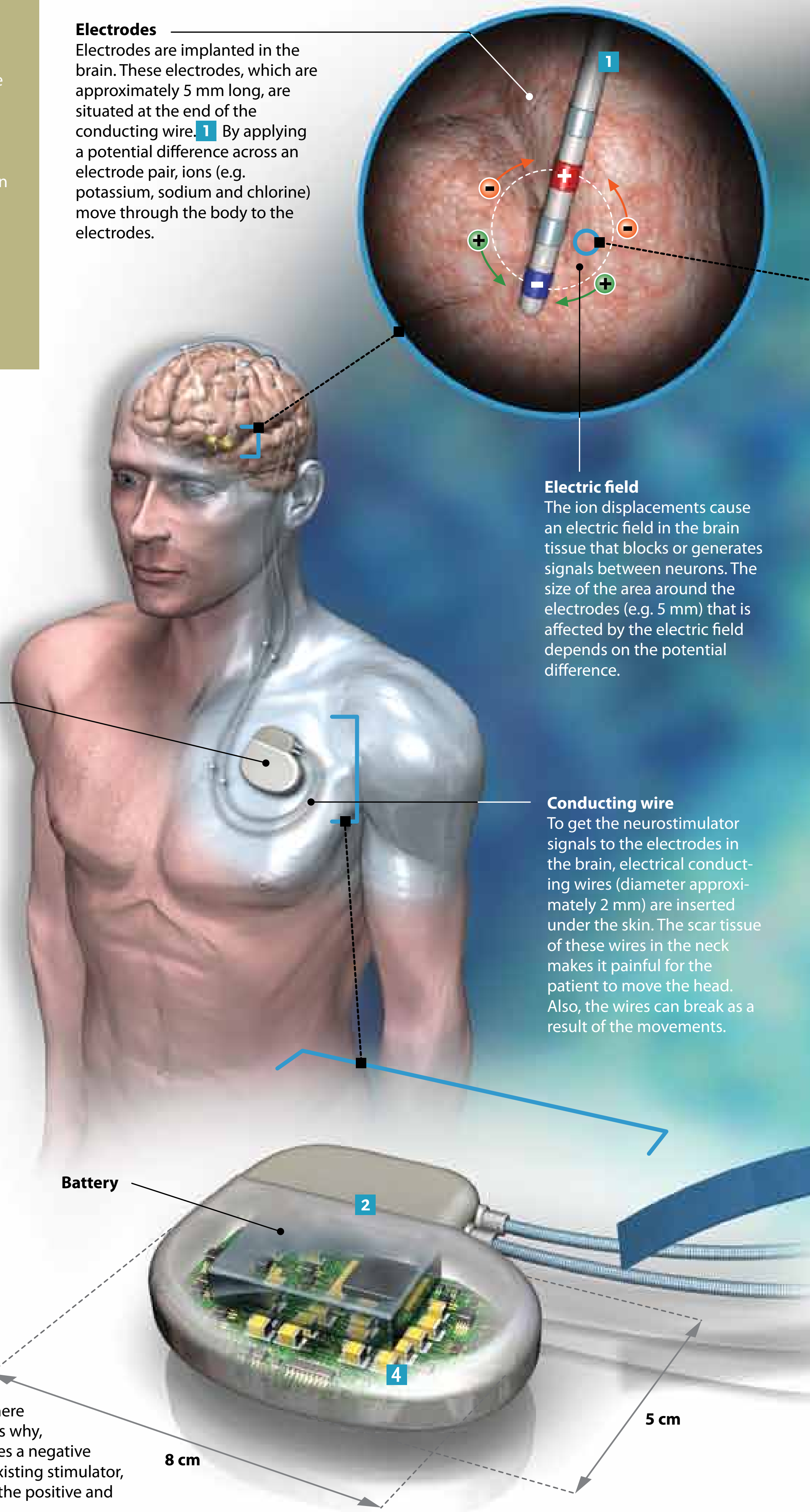
Brain stimulation

It is possible to suppress the effects of brain disorders such as Parkinson's disease by correcting abnormal pulse patterns in the brain between neurons. As soon as an electric field is generated in the brain, the effects of the disease disappear. However, the development of such neurostimulation is still in its infancy. The electrical parameters have been determined through trial and error and it is still not clear how the suppression exactly works.

Electrodes

Electrodes are implanted in the brain. These electrodes, which are approximately 5 mm long, are situated at the end of the conducting wire. 1 By applying a potential difference across an electrode pair, ions (e.g. potassium, sodium and chlorine) move through the body to the electrodes.



Undesired side effects

As different functional areas in the brain are close together, there is a chance that not only the target area will be stimulated. The result is that undesired side effects can occur. For example, a patient can be troubled by undesired mood changes with the suppression of Parkinson's disease because the brain areas that are responsible for this are close by.

Existing neurostimulator 2

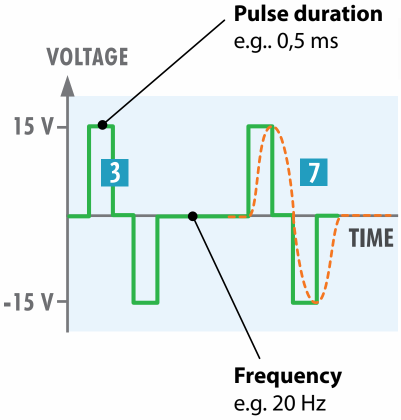
The neurostimulator sends electrical pulses 3 to the brain to affect the working of the brain. Currently available neurostimulators consist of a titanium case with a printed circuit board with electronic components, a battery and a number of capacitors. The neurostimulator does not fit in the brainpan 4 and is therefore placed under the skin in the chest.

Electric field

The ion displacements cause an electric field in the brain tissue that blocks or generates signals between neurons. The size of the area around the electrodes (e.g. 5 mm) that is affected by the electric field depends on the potential difference.

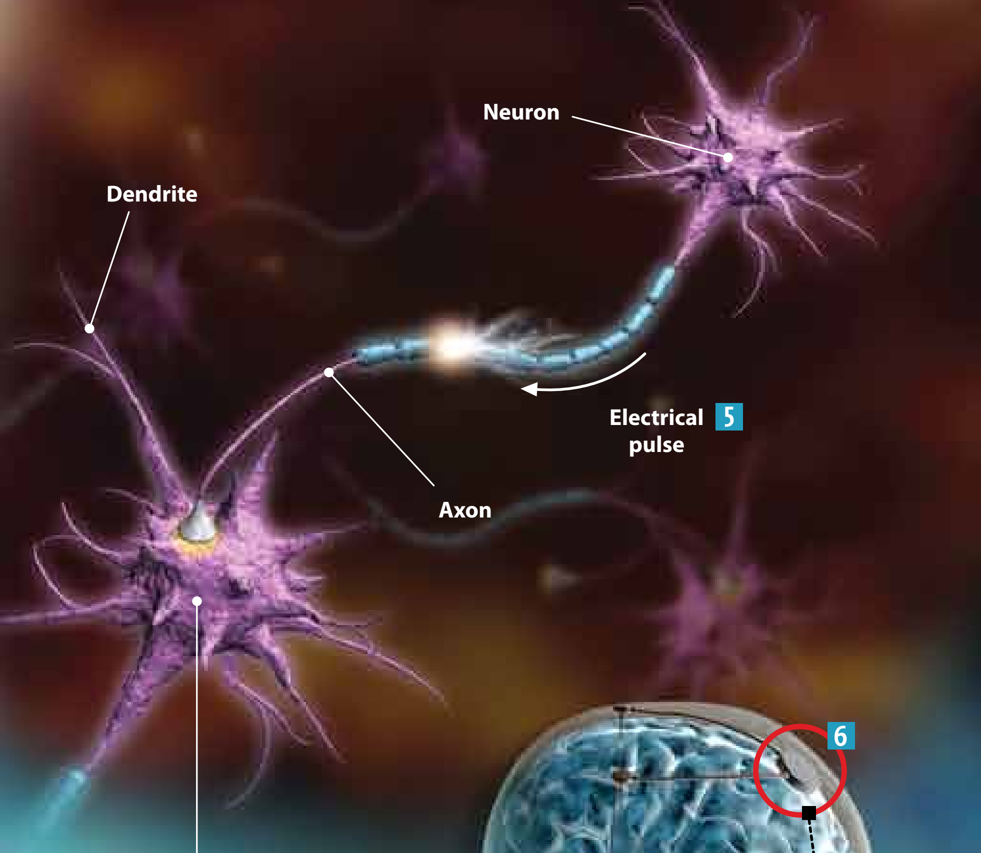
Conducting wire

To get the neurostimulator signals to the electrodes in the brain, electrical conducting wires (diameter approximately 2 mm) are inserted under the skin. The scar tissue of these wires in the neck makes it painful for the patient to move the head. Also, the wires can break as a result of the movements.



Balancing the charge

If electrons were to remain on the electrodes, undesired chemical reactions could occur that are dangerous for the brain. For example, metal ions could start to react with brain tissue. It is therefore essential that there is no build-up of charge at the electrodes. That's why, after a positive pulse, the stimulator always gives a negative pulse that removes all built-up charge. In the existing stimulator, large capacitors 4 are required to ensure that the positive and negative charges are exactly the same.



Electrical pulses
Neurons communicate with each other by means of short electrical pulses. 5 A neuron sends such a pulse (approximately 100 mV, pulse duration 5 ms) by applying a potential difference between the inside and the outside of the shell of the nerve cell, the cell membrane. This potential difference allows charged particles to move through the insulating cell membrane. As a result, there is a potential difference in the cell membrane of the adjacent cell. This action potential moves like a wave from one cell to another through a nerve fibre until the pulse has reached the core of the other neuron.

Billions of neurons
The brain of an adult person contains an estimated 100 billion neurons (nerve cells). A neuron receives information through a network that sometimes contains thousands of fibres, the dendrites. A neuron has one fibre, the axon, to send a signal to another neuron, gland or muscle.

NEW NEUROSTIMULATOR

Variable electrical signal

The present stimulator continuously generates a fixed, rectangular wave signal. However, brain tissue appears to adapt to a constant signal. Consequently, the effect of the stimulation reduces and the symptoms of the disease return after a few weeks. It is expected that a stimulator with a variable signal, 7 e.g. one that better resembles the signals that the brain tissue generates itself, will lead to a more effective treatment.

NEW NEUROSTIMULATOR

Approximately 50 times smaller volume

Within ten years' time, the Delft research group wants to make a neurostimulator the size of two 2 euro coins that can be implanted in the head. 6 In order to substantially reduce the size of the battery, the new design must be very energy efficient. The 16 capacitors can be left out because smart electronic circuits monitor exactly how much charge goes into and out of the brain.

8 Small battery
The battery must work for 20 years or must be capable of being remotely recharged (inductively).

Microcontroller
All components are integrated on a 5x5 mm^2 chip and controlled centrally by a microcontroller.

Actuator electronics
Control of the variable pulses that the electrodes send to the brains.

Sensor electronics
Processing the data registered by the sensors.

Wireless communication
An antenna communicates with the outside world so that the settings of the stimulator can be changed.

NEW NEUROSTIMULATOR

Only stimulate when necessary

The new stimulator must monitor the electrical activity of the brain through the electrodes and, based on this, decide when stimulation is required and in which areas. The energy consumption of the stimulator can only be substantially reduced by sending incidental pulses (at a lower voltage and with a shorter pulse duration).