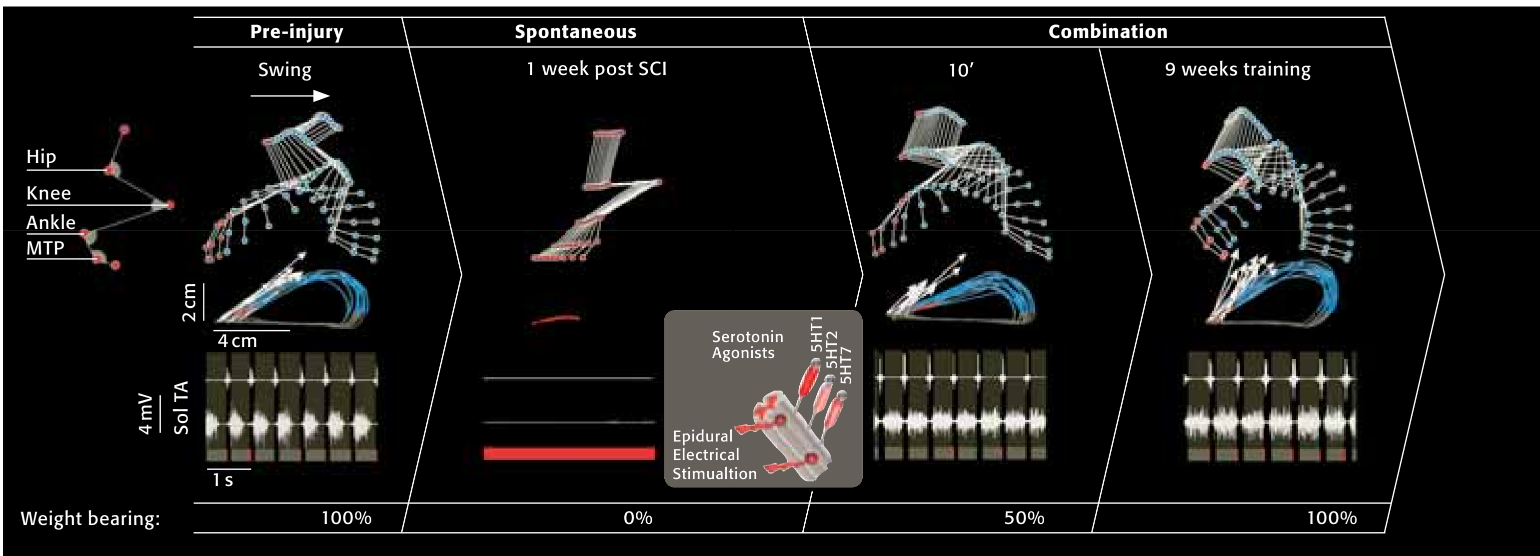
Treading lightly:
drug-electrical treatment allows paralyzed rats to walk again

Individuals who are wheelchair-bound after spinal injuries may regain some of their mobility through a combination of electric stimulation, drugs, and treadmill training. Findings by researchers in Zurich, Switzerland and the University of California in Los Angeles suggest viable clinical application within the next five years.



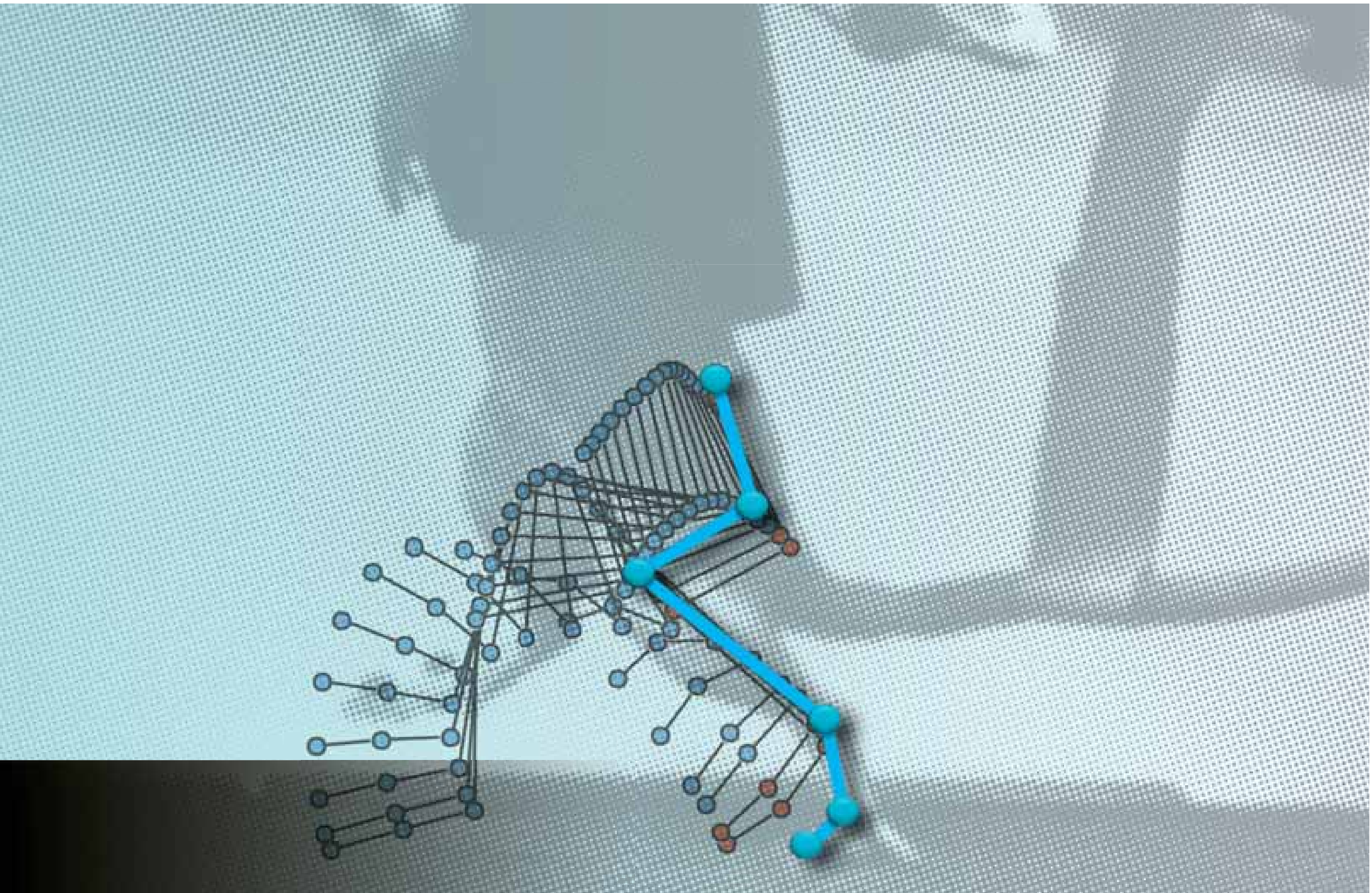
A stick diagram presents the whole swing phase/trajectory of the rats hind limb at the Lehman point: before the injury, one week after the injury, ten minutes after electrical and pharmacological stimulation, and after nine weeks of training.

Severe spinal cord injuries that eliminate all input from the brainstem induce permanent paralysis of the legs in rats and humans. Circuits in the lumbosacral spinal cord, also known as central pattern generators (CPGs), however, are able to generate movement without the help of the brain, and this is what several scientific studies in the past few years have focused on.

Past approaches have involved the separate activation of lumbosacral spinal circuits by electrical stimulation and pharmacology, with some success: both treatments induced rhythmic hind-leg movements. The animals, though, could not support their body weight, and showed variable movement.

Two treatments in tandem

Neurobiologist Grégoire Courtine of the University of Zurich, Switzerland, has now advanced to using the two treatments in tandem. He and his colleagues injected paralysed rats with specific agonists of the neurotransmitter serotonin to stimulate a subset of serotonin receptors which have been known to be involved in controlling distinct aspects of taking steps.



Paralysed rats have been made to sprint on treadmills through a combination of electrical and pharmacological stimulation. (The blue stick diagram highlights the hind-limb motions.)

Moreover, the researchers placed chronic electrodes on the dorsal surface of the spinal cord at different locations to stimulate the animals' spinal circuitry with continuous bursts of electricity. The electrical stimulation mimicked descending signals from the brain, thus reactivating the rat's paralysed hind legs.

Proof in the treadmill

As soon as one week after a spinal lesion, rats were able to walk on a treadmill, showing coordinated, albeit slow, weak and not weight-bearing movement. The rats were then trained by therapists under robotically-controlled support conditions with the aim of correcting their movement in case of imbalance or limb-crossing and showing them near-optimal locomotion. The spinal cord was thus "learning by doing" and by being presented with a repetitive source of correct sensory input.

After two months of training, the rats could bear their own weight and were able to walk, sprint, step sideways, and jog backwards on the treadmill, responding swiftly to changes in pace and direction. What could be observed was in fact a functional remodelling of the circuits in the spinal cord, which translated into an improved capacity of the spinal cord to coordinate the recruitment of the muscles to step: the spinal cord became more efficacious in performing locomotion successfully.

The improvement was not permanent, though: the rats could only walk with electrical and pharmacological stimulation and didn't recover their sense of balance.

Developing a neuroprosthesis

Based on this research, Courtine and his colleagues are now working on a project called "Rewalk" (see interview) which aims at developing a neuroprosthesis that electrically stimulates the lumbosacral spinal circuits in individuals with spinal cord injuries, hence improving their capacities to regain part of their mobility.
"Rewalk" has been set up by a network of nine different university and private laboratories in Italy, Germany, Switzerland, France, England, and Finland, with about thirty neuroscientists involved. Planned as a four year project, Courtine and his team hope that within the next few years, the neuroprosthesis will be technically developed enough and approved to start trials in humans.

Interview

with Grégoire Courtine, neurobiologist at University of Zurich, Switzerland

What is the significance of your recent research?

We have shown that rats can walk or run without a connection to the brain, although it requires outside intervention to make it happen. This hasn't been shown to this extent before, and proves that in the lower spinal cord there is all the necessary circuitry to generate locomotion. Our approach transforms the non-functional, dormant spinal cord into a locomotor-permissive state, in which spinal motor networks are ready to process sensory input to coordinate stepping. The spinal circuitry integrates sensory information like load, stretching of the muscles and shifting of weight, and is hence able to generate flexible locomotion. This opens new avenues for the design of useful clinical applications to improve the recovery of locomotion in individuals with spinal cord injury.

How did you get the idea of the combined approach?

It was an obvious step. We started several years ago by testing electrical stimulation, training and the use of pharmacology on rats, stimulating their lumbosacral spinal circuits in different ways. Our current research was building on our expertise, bringing together what we have known to be efficacious. However, the powerful synergy between these different approaches was a real surprise.

With your technique will paraplegics eventually be able to walk again?

For individuals with complete spinal cord injuries it is a complicated challenge but there are reasons to hope that we can facilitate recovery of locomotion in individuals with severe incomplete spinal injuries, that is, for individuals who still have some voluntary control over their movements but not enough to walk independently. Electrical stimulation, training and pharmacology have all been shown to be efficacious in human beings, not only rats. We will have to optimize the methods for humans, combine them and expect a synergetic effect. We cannot hope to restore normal locomotion, but develop useful alternative strategies to regain some walking capacities. Instead of being wheelchair-bound, the individuals may recover the capacity to move with the help of walkers.

Why do you consistently not use the term "central pattern generators", CPGs, in your research paper?

The idea of CPGs is a convenient notion but reductive. It presents the lumbosacral neural network as simple, with the main function of controlling alternatively the flexor and the extensor muscles, or, in other words, as a stereotypical network generating stereotypical output. It also presents it as "hardwire" and established ontogenetically. In our research, however, we have observed a smart system which is able to learn without brain input, to make decisions about how the muscles should be activated to walk, and to continuously meet the requirements of the task. It is highly plastic and can be remodelled functionally, which we observed in connection with our treadmill training. I actually call the lumbosacral neural network the "spinal brain". If it is not used, that is, if a patient only sits in a wheelchair after a lesion, it loses its capacity. So it's very important to take care of the spinal cord networks soon after the injury.

And this is what your neuroprosthesis "Rewalk" does? What does your neuroprosthesis project "Rewalk" imply?

Our team is working on a wireless-controlled implant, basically a set of electrodes, which would be inserted between the spinal cord and the vertebrae below a lesion, where it would deliver electrical impulses to stimulate and activate the circuits. The size would be roughly 5 cm x 1 cm, with a thickness of 200 micromillimeters, the material being highly flexible and biocompatible. The material of the electrodes is a secret as the patent is pending. In regards to the power supply, I can only say that the idea is to develop a fully internal system. To prepare the circuits we may also try to use part of the pharmacology in patients and surely train the patients on a treadmill. Our collaborators in Zurich lead the Paraplegic Centre who developed the rehabilitation robot "Lokomat." This unique environment may greatly facilitate the translation of our work.

Do you anticipate a costly device?

The equipment should not be too expensive, it isn't so complex once it is developed, and we expect the European Union to support this initial phase. There already are existing electrode arrays that have been developed for the management of pain in legs and back, which are around USD $10,000. But of course surgery for implantation will be expensive as well as the subsequent therapy.

What are your hopes for this technology?

We hope that we can reach viable clinical applications within the next couple of years. Our project "Rewalk" is paving the way, but we aren't there yet.

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