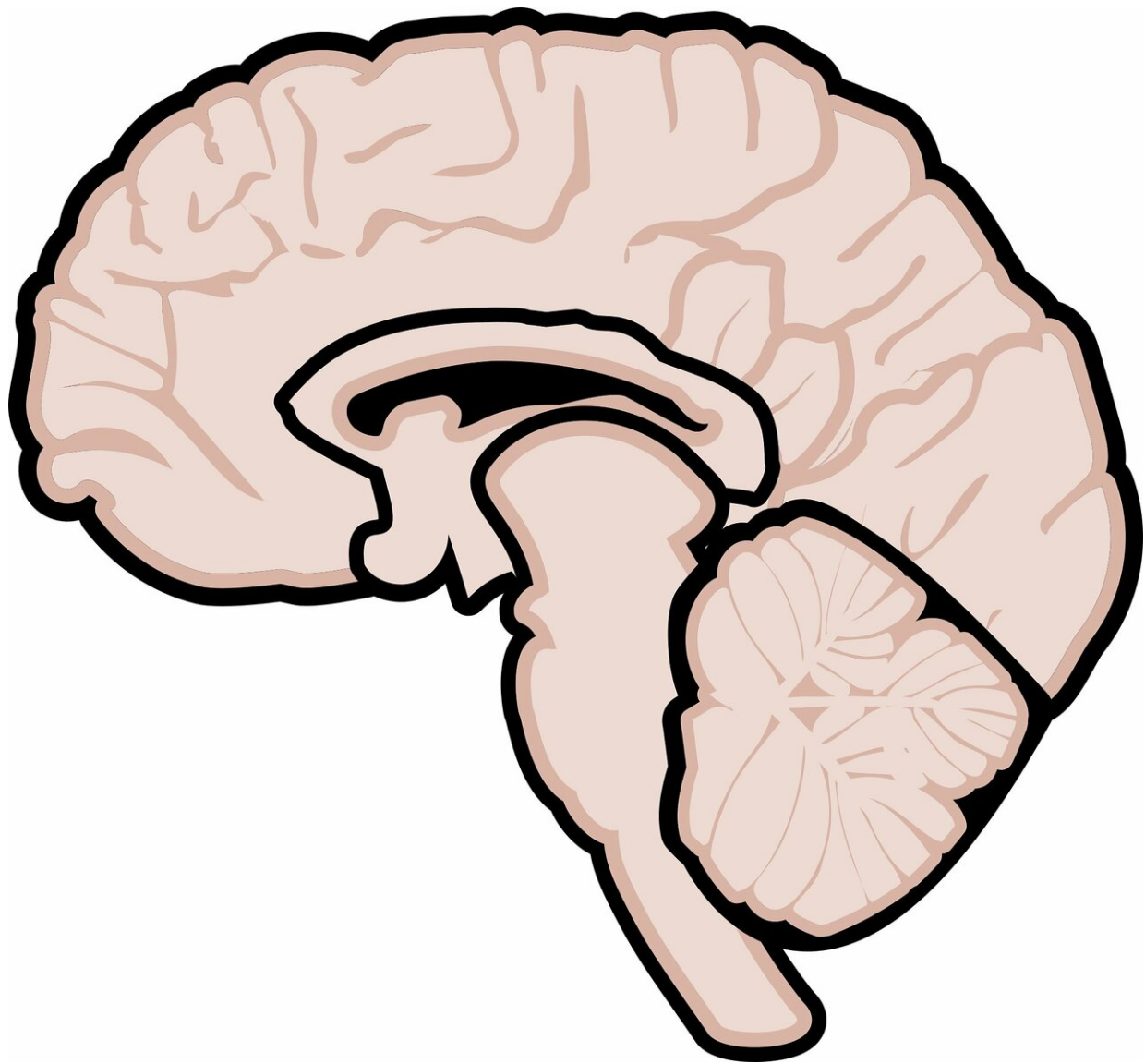


Perilous ruptures described in a multiple sclerosis model

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The permanent neurological deficits of multiple sclerosis patients largely depend on the extent of degeneration of long nerve fibers. The latter is initiated by ruptures in the cell membrane and the resulting influx of calcium ions.

In Germany alone, more than 200,000 patients suffer from multiple sclerosis (MS). MS is an [autoimmune condition](#) and one of the most common inflammatory diseases of the central nervous system. The degree of the patient's disability, is critically dependent on the extent of nerve-fiber loss. This is because the autoimmune reaction characteristic of the condition attacks the long processes, called axons, which are responsible for the transmission of nerve impulses. Now a team led by Professor Martin Kerschensteiner, Director of the Institute of Clinical Neuroimmunology at Ludwig-Maximilians-Universitaet (LMU) in Munich, and Professor Thomas Misgeld of the Institute for Neuronal Cell Biology at the Technical University of Munich (TUM), working with an animal model of MS has identified a putative mechanism that can result in the degeneration of axons. They have shown that minuscule ruptures in the cell membrane allow [calcium ions](#) to percolate into the neuron, disrupting the ionic balance and ultimately killing the axon. The new findings appear in the journal *Neuron*.

In previous studies, Kerschensteiner, Misgeld and colleagues had observed that axons in inflammatory lesions often were swollen and subsequently fragmented. "But in some cases, the swelling spontaneously regressed and these axons recovered," says Kerschensteiner. "So the process is in principle reversible, and could perhaps be therapeutically modulated if we had a better understanding of the underlying mechanisms." With the aid of in-vivo microscopy, the researchers have now shown in an animal model of MS that the fate of these axons depends on their [calcium](#) content. Axons with an abnormally high

concentration of calcium are more likely to undergo swelling and subsequent degeneration and less likely to recover from this state than axons with normal levels of the ion. "Strikingly, these changes begin relatively early in the course of the axon damage process," says Misgeld. Indeed, in 10% of the axons examined, the calcium concentration was already increased prior to the onset of swelling. About half of the swollen axons were found to have high levels of intracellular calcium, and a correspondingly high risk of [degeneration](#).

The excess calcium is derived from the extracellular space and it enters the axon via nanoruptures in the cell membrane, as the team was able to demonstrate using a fluorescent dye coupled to a macromolecule. "The complex is too large to penetrate into an intact axon. Only if the [membrane](#) has been damaged can it be taken up into the axon and detected by its fluorescence. With the aid of in-vivo microscopy, we were also able to show that many of the [axons](#) that take up the dye also contain increased amounts of calcium," says Kerschensteiner. "The fact that, in the inflamed nervous system, tears in the [cell membrane](#) can contribute to the death of nerve fibers is a new discovery, which could in future be therapeutically relevant." adds Misgeld. It is already known from studies of spinal cord injury that nerve [cells](#) have the capacity to repair ruptures caused by mechanical forces. The researchers therefore hope that a better understanding of the origins and repair of damaged nerve-cell membranes will bring them closer to identifying new targets for therapeutic interventions.

More information: Calcium Influx through Plasma-Membrane Nanoruptures Drives Axon Degeneration in a Model of Multiple Sclerosis. *Neuron*. DOI: doi.org/10.1016/j.neuron.2018.12.023

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