Neural membrane's structural instability may trigger multiple sclerosis

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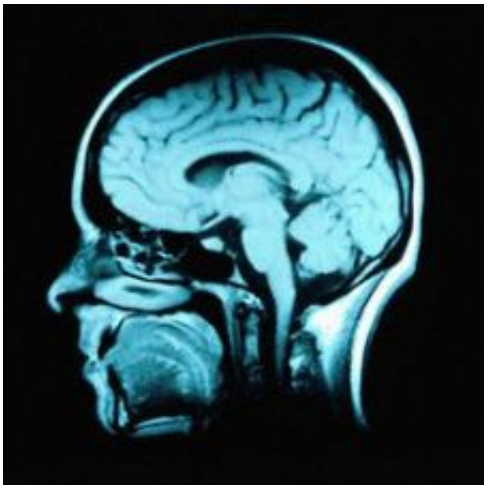

Credit: Tel Aviv University

Multiple sclerosis is one of the most devastating neurodegenerative diseases. It affects some 2.5 million people worldwide. It has no known cure.

Until now, researchers have speculated that the body's own immune system was unleashing an uncontrolled attack on myelin sheaths—our neurons' protective shield—that was largely responsible for the sudden outbreak of the disease.

But a new Tel Aviv University study published in the *Journal of the American Chemical Society* (*JACS*) pinpoints a structural instability in the

myelin membranes, the "insulating tape" surrounding neurons. This vulnerability affords the immune system—and its attacks—access to otherwise protected regions.

"We found that small modifications in the myelin sheaths create structural instabilities that may help the immune system to enter and attack neurons," said Prof. Roy Beck, the study's principal investigator, of TAU's School of Physics and Astronomy and Sagol School of Neurosciences. "Current therapeutic approaches have focused on the autoimmune response without identifying a clear mechanism. Our research suggests a new avenue for multiple sclerosis therapies and diagnostics."

Breaking down the insulation

Our axons, which carry electrical impulses in neurons, are surrounded by protective myelin sheaths. In multiple sclerosis, an autoimmune catastrophe, these sheaths break down and are misidentified as hostile foreign entities, which the immune system then attacks.

The research, conducted by Rona Shaharabani, a doctoral student in Prof. Beck's lab, pinpoints the precise alterations to the myelin sheaths that result in structural instabilities, creating "easy access" for autoimmune attacks. "After years of research, we were amazed to discover that a possible trigger for the outbreak of the disease could be found in the membrane's physical structure," said Prof. Beck.

According to Prof. Beck, the lipid are the main building blocks of the myelin sheaths. As such their shape has a critical impact on the resulting self-assembled membrane structure. "If the basic building blocks are straight, the membrane will be flat, which is the preferred structure for a neuron's 'insulating tape,'" said Prof. Beck. "However, if they exhibit a more cone-like shape, the membrane will tend to form closed round

cylinders. These produce spontaneous holes in the surface of the sheath, rendering it vulnerable to attack."

For the purpose of the research, the scientists harnessed X-ray light to examine hundreds of membrane model systems that mimicked those of healthy and diseased animal models. In collaboration with Prof. Ruth Arnon of the Weizmann Institute, co-developer of the leading MS drug Copaxone, and Prof. Yeshayahu Talmon of the Technion - Israel Institute of Technology, the team also used electron microscopy to determine the different nanoscopic structures of both natural myelin sheaths and model system membranes.

"The next step is to find a way to reverse the disease progression and find new techniques for early detection," said Prof. Beck.

More information: Rona Shaharabani et al, Structural Transition in Myelin Membrane as Initiator of Multiple Sclerosis, *Journal of the American Chemical Society* (2016). DOI: 10.1021/jacs.6b04826

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