# Mechanism behind upper motor degeneration revealed

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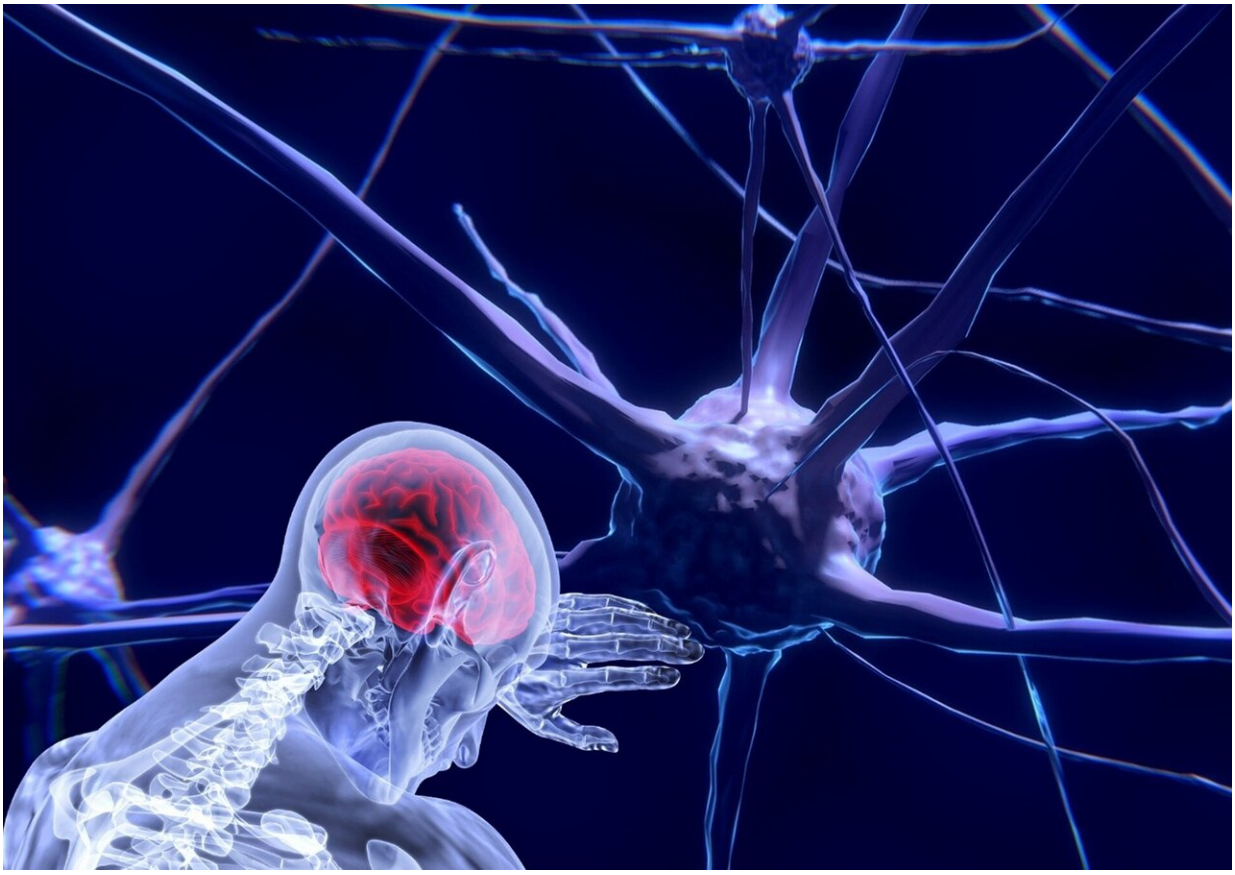

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Scientists from Northwestern Medicine and the University of Belgrade have pinpointed the electrophysiological mechanism behind upper motor

neuron (UMN) disease, unlocking the door to potential treatments for amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases, such as Hereditary Spastic Paraplegia and Primary Lateral Sclerosis.

The study, published in *Frontiers in Molecular Neuroscience* on May 19, 2020, reveals the molecular underpinnings of electrical signals from potassium and sodium ion channels within the neuron's cell membrane.

Maintaining stability is the primary goal of healthy UNMs. Without it, cells begin to degenerate. Like the game of telephone, when UMNs process signals from neighboring neurons incorrectly, the message fails to reach the motor neurons in the spine, which instruct muscles to move.

"Voltage-gated ion channels, as a family, are involved in many neurodegenerative diseases, but their function, modulation, and expression profile are very complicated," said senior study author Hande Ozdinler, associate professor of neurology at Northwestern University Feinberg School of Medicine.

To identify the precise areas within the ion channels where the dysfunction began, the investigators, led by Dr. Marco Martina, associate professor of physiology and of psychiatry and behavioral sciences at Feinberg, recorded the electrical signals of in vivo cells in the earliest stage of ALS to measure the neuron's reaction to external stimuli. The team also looked at the genes of the diseased UMNs' ion channels to measure the changes in the structure of the ion and its subunits to determine whether the cause of degeneration was intrinsic.

The data revealed that early in the disease UMNs were unable to maintain the balance of excitation and inhibition within the cortical circuitry and their behavior was due to dynamic changes in key ion channels and their subunits.

"We all knew that ion channels were important, but we did not know which subunit or ion channels were important or involved in the shifting balance from health to disease in UMNs," said Ozdinler, a member of the Chemistry of Life Processes Institute. "When we received the exon microarray results, it was obvious that the ion channels were perturbed very early in the disease, potentially initiating the first wave of vulnerability."

By identifying the molecular underpinnings of the early stages of neurodegeneration, the study also identified potential targets for future treatment strategies.

"There are already drugs out there for some of those ion channels and subunits, but we never thought that we could use them for ALS because we did not know the mechanism," said Ozdinler. "This is the information we needed to move forward. "Now, we may begin to investigate whether we can utilize some of these drugs, already approved by the FDA, for motor neuron diseases."

**More information:** Javier H. Jara et al. The Electrophysiological Determinants of Corticospinal Motor Neuron Vulnerability in ALS, *Frontiers in Molecular Neuroscience* (2020). DOI: 10.3389/fnmol.2020.00073

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