Researchers pinpoint neurochemical marker linked with loss of motor function in ALS

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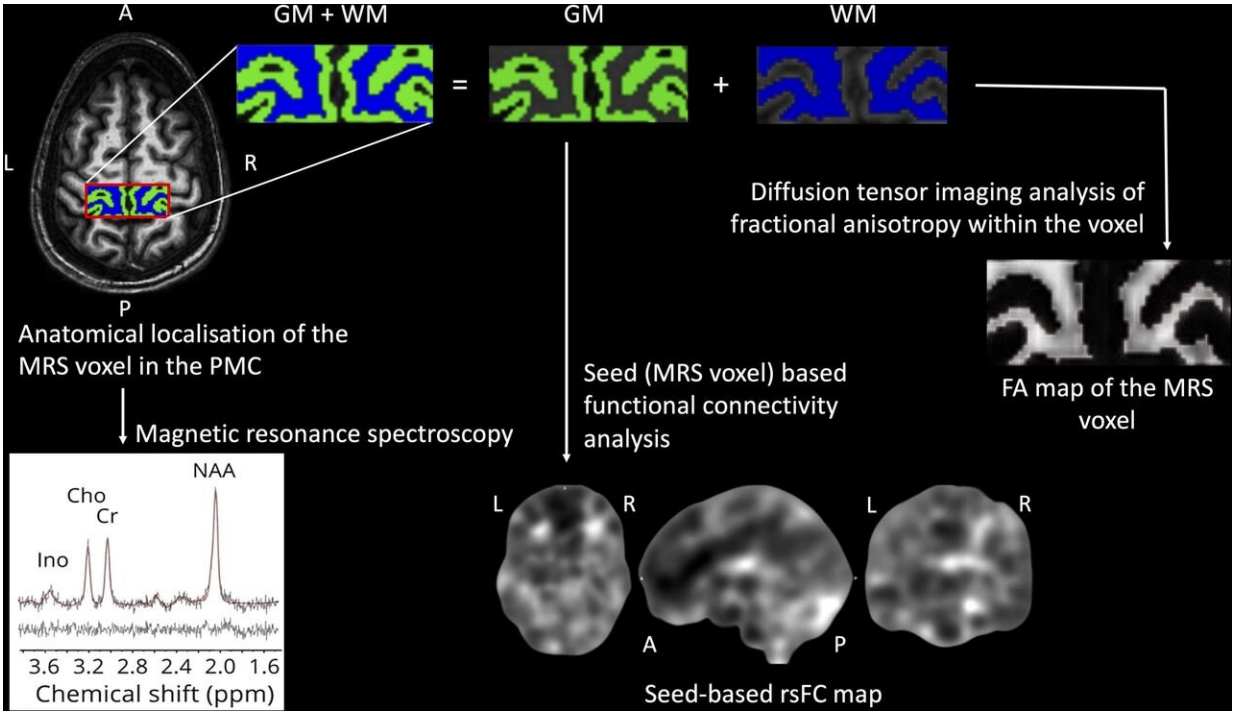

Overview of the processing pipeline. Spectral signatures of neurometabolites of interest were obtained from the primary motor cortex (PMC) (magnetic resonance spectroscopy (MRS)) voxel. The MRS voxel underwent segmentation into gray matter (GM) and white matter (WM) tissue classes, which respectively underwent analyses of functional connectivity and diffusion tensor imaging. FA, fractional anisotropy; rsFC, resting-state functional connectivity. Credit: *Journal of Neurology, Neurosurgery & Psychiatry* (2022). DOI: 10.1136/jnnp-2022-329993

University of Alberta researchers have identified a neurochemical marker related to the loss of motor function and communication breakdown between the primary motor cortex—the part of the brain that controls our muscles—and the rest of the brain in ALS patients. Knowing this, they're now aiming to find out whether the marker might also offer a test to evaluate new treatments to improve brain function.

The study, "Motor cortex functional connectivity is associated with underlying neurochemistry in ALS," was published in the *Journal of Neurology, Neurosurgery & Psychiatry*.

Amyotrophic lateral sclerosis, or Lou Gehrig's disease, is a terminal neurological disease. As motor neurons fail, the primary motor cortex loses the ability to communicate with muscles—and as it turns out, the rest of the brain—resulting in muscle stiffness and weakness. Eventually the brain loses the ability to communicate with muscles essential to our survival.

Studies have shown that the drug riluzole can improve patients' life expectancy, and also that levels of N-acetylaspartate (NAA), a neurochemical associated with healthy neurons, increase with use of the drug. NAA is the same neurochemical that Sanjay Kalra and his team have identified as an ALS marker.

Now Kalra wonders whether the reverse is true. "We'd like to know in future studies if improving neurochemistry with medication will improve functional connectivity," he says.

Avyarthana Dey, a Ph.D. student in the Faculty of Medicine & Dentistry and the Neuroscience and Mental Health Institute and lead author of the study, says she also wants to know whether the increased NAA levels seen with riluzole will correlate with improved survival.

"And if it does, by how much? Because right now riluzole has been shown to increase survival of patients by three to six months on average, but we don't know exactly how it does that," she notes.

Identifying the marker

Kalra is a neurologist and professor in the Division of Neurology, the Henri M. Toupin Chair in Neurological Sciences and a member of the Neuroscience and Mental Health Institute. He's also director of the Comprehensive Analysis Platform to Understand, Remedy, and Eliminate ALS (CAPTURE ALS) and the Canadian ALS Neuroimaging Consortium (CALSNIC), which played an important role in the new study.

The researchers analyzed data collected from five Canadian university hospitals, all part of CALSNIC: the U of A, University of Calgary, McGill University, University of Toronto and University of British Columbia.

"One of the things that impedes research in single-center studies is that we only have a very small sample," says Dey. "Having five different centers can capture a wider population with a more varied disease pattern."

Together the five sites recruited 52 patients with ALS and 52 healthy controls. Foot tapping frequency was recorded for each patient and was significantly reduced in ALS patients. Of the 52 patients, 48 also showed overly responsive tendon reflexes, 21 showed spasticity, a condition in which there is an an abnormal increase in muscle tone or stiffness of muscle, and 15 exhibited the Babinski sign, a foot reflex in which the big toe flexes up instead of down when the foot is stroked or scratched—a normal reflex in children up to two years old but not in older people.

Having established a loss of motor function among the ALS patients, the researchers then used functional MRI scans to measure how well the primary motor cortex was communicating with the rest of the brain. They also used two other tests to measure neurochemicals in the primary motor cortex and monitor the deterioration of white matter in the same area.

Their hypothesis was that in ALS the primary motor cortex can't communicate with the rest of the brain properly and that this is likely due to underlying problems with either the structure or neurochemistry of the upper motor neurons. These neurons are located in the brain and travel all the way down to the spinal cord, where they communicate with lower motor neurons, which then communicate with the muscles.

"These upper motor neurons are thought to be more likely to be affected by the neurodegenerative process," says Dey. "Because of their big size, they're more vulnerable."

The researchers found that as motor function and the connection between the primary motor cortex and the rest of the brain deteriorated in ALS patients, so did the levels of NAA found in the motor cortex where the upper motor neurons originate. While they also found structural deterioration of the white matter, it did not directly correlate with the deterioration in communication.

"We postulate that the abnormality in NAA occurs before the occurrence of any apparent structural changes," says Dey.

A step toward a definitive test

The biggest challenge for researchers is that ALS affects each patient differently, and its symptoms can mimic those of other diseases and conditions, such as stroke or neuropathy.

"The process with ALS is very much, at this point, ruling out other conditions," says Kalra.

Unfortunately, while a decrease in NAA in the upper motor neurons may one day allow clinicians to have a definitive test for ALS, at present clinicians are not trained in the necessary imaging techniques.

"At this point brain imaging is not used in that way," says Kalra. "It remains very much a research tool."

A definitive test could lead to earlier diagnosis for patients, which would allow them to get treatment and support earlier.

"The earlier we can make the diagnosis, the sooner we can start therapies and start counseling, and the sooner we can provide opportunities for enrollment in clinical trials," explains Kalra.

The three drugs currently used to treat ALS also work better the earlier treatment begins, and they can slow the disease's progression and prolong life expectancy.

Kalra adds that an earlier diagnosis, even if it's a terminal diagnosis, can lead to some peace of mind for patients.

"It significantly reduces the anxiety, stress and panic that patients and their caregivers face when something is happening so quickly to them, when they're losing function, yet no one can come up with a diagnosis."

More information: Avyarthana Dey et al, Motor cortex functional connectivity is associated with underlying neurochemistry in ALS, *Journal of Neurology, Neurosurgery & Psychiatry* (2022). DOI: 10.1136/jnnp-2022-329993

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