Focus on early stage of illness may be key to treating ALS, study suggests

22 March 2018

Professor of neuroscience and Brown Institute for Brain Science researcher Justin Fallon (left) — pictured here with fellow Brown faculty member Eric Morrow — says the new study opens the way for developing new classes of drugs to combat ALS. Credit: Peter Goldberg

A new kind of genetically engineered mouse and an innovation in how to monitor those mice during research have shed new light on the early development of an inherited form of amyotrophic lateral sclerosis (ALS).

An international team of scientists, including four from Brown University, conducted and analyzed tests using a "knock-in" mouse carrying a gene for a mutant DNA/RNA binding protein called TDP-43, which causes a form of inherited ALS in humans.

In the study published in the journal *Nature Neuroscience*, the researchers found that behavioral, cognitive and structural dysfunctions in the new mouse model of ALS and a related disorder, frontotemporal dementia (FTD), were evident long before the neuronal degeneration that occurs late in these diseases. Many inhibitory neurons were lost early in the development of ALS, which is in sharp contrast to other degenerative diseases where most of the early losses are of excitatory neurons.

Thus, the results open the way to discover and test potential ALS therapies targeted at the early stages of the disease, when treatment is most likely to be effective.

"This study reveals new pathways in the earliest stages of ALS-FTD and opens the way for developing new classes of drugs to combat this dreadful disease," said Justin Fallon, a professor of neuroscience at Brown and researcher at the Brown Institute for Brain Science and one of the study authors.

The research is part of an effort to develop a more robust understanding of the early-stage defects in ALS neurons that precede loss of motor control. The results will be the basis of further research into the disease and have the potential to open the way to develop new therapies, the authors said.

Fallon said that in addition to the value of the findings themselves, the study demonstrates advances in creating animal models that can be used more successfully in mimicking the disease in ALS research, which is a key element in driving new research and possible therapies.

The new mice, created by researchers at King's College London and the University of Massachusetts Medical School, are particularly strong in showing early changes connected to the development of ALS, Fallon said. Just as significantly, a new artificial intelligence technology developed at Brown allowed the researchers to monitor and analyze mouse behavior and proved instrumental in generating the findings.

In research, monitoring and analysis of animal model behavior is often a stumbling block because it is difficult to do consistently and efficiently, Fallon said. In this study, mice were monitored 24 hours a

day for stretches of five days. The use of the Automated Continuous Behavioral Monitoring (ACBM) system designed by Thomas Serre, an associate professor of cognitive, linguistic, and psychological sciences at Brown, made that work much more efficient.

The system—a computational analysis tool that assigns behavior to individual frames of video—allowed for the sensitive, effective and efficient scrutiny of millions of video frames. Amanda Duffy, a Brown Ph.D. student in Fallon's lab, suggested that Serre's system be tried in the study; another study author, Youssef Barhomi, was a research engineer in Serre's lab.

"We were able to get an accurate and deep accounting of the behavior of these mice," Fallon said, "We've now opened up a new way of analyzing mice behavior."

That new method for analysis could become a standard way of phenotyping mice, Fallon said, and the ACBM system is now in use in other research at Brown on ALS, and inquiries about the system have started to come from beyond campus, he added.

Fallon also noted that in the study, the knock-in mouse made it possible to see that abnormally high levels of TDP-43 protein were being made. A key next step in the ALS investigation will be to identify the pathways that lead to loss of the inhibitory neurons and the behavioral defects.

More information: TDP-43 gains function due to perturbed autoregulation in a Tardbp knock-in mouse model of ALS-FTD. *Nature Neuroscience* (2018) DOI: 10.1038/s41593-018-0113-5

Provided by Brown University