Songbirds pinpoint effects of Huntington's disease

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Zebra finches, like this male and female pair (*Taeniopygia guttata*), are being used to study the effects of mutations in the gene behind Huntington's disease in humans. Credit: Keith Gerstung, via Wikimedia Commons

Although Huntington's disease is caused by mutations in a single gene,

understanding how it ravages the brain and body has been anything but simple.

A new study by Duke University scientists parses the role of the Huntington's disease gene in an area of the brain responsible for complex, sequential movements like those used to talk to a friend, play the violin, or swing a golf club.

Described March 7 in the *Proceedings of the National Academy of Sciences*, the findings not only give a clearer view of how the genetic mutation that causes Huntington's disease alters brain and behavior, it may also offer a new therapeutic target for treatment.

"These new results make a direct link between the genetic mutation, the insults that mutation causes to brain structure and function, and the behavioral pathology," said Richard Mooney, the George Barth Geller Professor of Neurobiology in the Duke School of Medicine.

Last year, researchers at the Rockefeller University in New York described a genetically altered songbird that shows an array of symptoms reminiscent of Huntington's disease, such as tremor, body stiffness and difficulties vocalizing.

The songbird is ideal for studying Huntington's disease, Mooney said, because of the way evolution has enhanced the regions of its brain that are important in learning and singing songs. A song is produced by a string of precise movements of the vocal and respiratory muscles. Because each bird normally sings the same way every time, researchers can easily measure and detect subtle changes to the birds' movements caused by a faulty gene.

The Rockefeller group expressed the mutated gene throughout the entire brain and body of the songbird, affecting many behaviors. That made it

difficult to draw direct connections between the genetic mutation, specific brain changes, and problems making complex movements.

In the new study, using the same species of songbird, Mooney's group introduced the mutated gene in just one region of the brain called the basal ganglia, which is especially vulnerable to the disease.

Buried deep in the brain, the basal ganglia comprise a network of nerve cells that help start and stop movements and organize sequences of actions. The researchers introduced the Huntington's disease gene only in a small region of the basal ganglia called 'area X', which is important for learning and singing songs in birds.

Within two months of receiving the virus carrying the gene mutation, the songbirds sang abnormal songs, and more songs in general, compared to healthy birds. The syllables of the songs were normal, but as with people with Huntington's disease, the birds had trouble producing syllables in the right order and halting their songs once they had started them.

The mutation affected a specific type of neuron (medium spiny neuron) in area X. Another type of neurons (pallidal), which are the main output neurons of the basal ganglia, survived. But the timing of the pallidal neurons' activity became unreliable when the study's lead author Masashi Tanaka, a postdoctoral associate in Mooney's lab, measured them in singing birds.

"That suggests that there's something lost in the complexity of the signals that these output neurons normally transmit," said Mooney, who is a member of the Duke Institute for Brain Sciences. "If that's the case, then you could imagine that if you reinstituted more complex patterns of activity, that may be sufficient to restore normal behavior."

The researchers also found that shutting off the main output of area X

was sufficient to restore normal songs in the birds. It may be that no output from the basal ganglia is better than the wrong kind, Mooney said.

Mooney's team has anecdotally observed that with time, a small subset of the songbirds stabilize their songs. They don't recover completely, but their songs show fewer abnormalities. Mooney hopes to understand why. It could be because adult songbirds can generate new medium spiny neurons, unlike humans.

"If new neurons drive recovery, it may be that the songbird will provide a model for understanding how neural replacement in humans can be used to drive behavioral recovery in a range of neurodegenerative diseases," Mooney said.

More information: Focal expression of mutant huntingtin in the songbird basal ganglia disrupts cortico-basal ganglia networks and vocal sequences, *Proceedings of the National Academy of Sciences*, www.pnas.org/cgi/doi/10.1073/pnas.1523754113

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