Early training delays symptom onset in mouse model of Rett syndrome

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New scientific findings bring hope that early training during the presymptomatic phase could help individuals with Rett syndrome, a neurodevelopmental disorder, retain specific motor and memory skills and delay the onset of the condition. Researchers at Baylor College of Medicine and the Jan and Dan Duncan Neurological Research Institute

at Texas Children's Hospital reported in the journal *Nature* that, in a mouse model of Rett syndrome, intensive training beginning before symptoms appear dramatically improved the performance of specific motor and memory tasks and substantially delayed the appearance of symptoms.

The researchers propose that newborn genetic testing for Rett syndrome, followed by prompt intensive training in the skills that will be affected, such as gait/balance, manual dexterity and communication, may alter the course of the condition in ways that would improve the patients' quality of life and prepare them for later therapies.

"Years ago, I decided to study Rett syndrome because it struck me as a neurological condition like no other I had seen before," said corresponding author Dr. Huda Zoghbi, Ralph D. Feigin, M.D. Endowed Chair and professor of molecular and human genetics, pediatrics and neuroscience at Baylor. Zoghbi also is the director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital.

Rett syndrome is a rare, devastating neurological disorder that results in varying degrees of mental and motor disability, primarily in girls. There are no effective treatments.

"What I saw with Rett syndrome was that girls with the condition were born looking like any other healthy baby and developed as expected during their first year," said Zoghbi, an investigator at the Howard Hughes Medical Institute and a member of Baylor's Dan L Duncan Comprehensive Cancer Center. "However, when the girls reached one or two years of age, they gradually lost the skills they had developed—they began to have trouble walking and with balance, slowly lost their ability to communicate and started to wring their hands constantly. The condition then stabilizes, but the girls remain disabled for the rest of their lives."

In a 1999 report, the Zoghbi lab was the first to show that mutations in the X-linked gene MECP2 cause Rett syndrome. Since then, the lab has continued not only to improve our understanding of this complex condition, but also, as in the current report, to provide hope through research that opens new possibilities to improve the lives of girls with the syndrome.

Early training delays onset of symptoms

Although there is no current effective treatment for Rett syndrome, previous work from the Zoghbi lab has shown that deep brain stimulation (DBS) can correct in animal models some of the symptoms, such as deficits in learning and memory. However, each symptom requires a specific DBS treatment, which implies that implementing this approach to treat the syndrome would be difficult.

Thinking along the lines of mimicking DBS, but in a less invasive way, the researchers investigated whether early intense training in specific tasks before the symptoms appeared would change the normal progression of the condition. Supporting this idea, studies in autism spectrum disorders (ASD), a condition that shares some symptoms with Rett syndrome, has shown that behavioral training can improve motor and cognitive skills in young children with ASD.

The researchers worked with Rett mice, a mouse model of Rett syndrome in which females lack one of the two Mecp2 genes, testing the effect of intensive training in a motor coordination task—walking forward on a rotating rod—on Rett syndrome progression.

"We show that there is a critical window in early life when intensive behavioral training significantly improves behavioral deficits. Mice that started their training early, weeks before symptom onset, dramatically improved their performance on that specific motor task when compared

with Rett mice that did not train," said first author Nathan P. Achilly, a student in Baylor's M.D./Ph.D. program in Developmental Biology working in the Zoghbi lab. "Importantly, we also learned that early training substantially delayed the onset of symptoms and that starting training after the symptoms appeared did not improve the performance."

Benefits are training-specific

"Intriguingly, training on a particular motor task did not have the same effect on other symptoms of the syndrome, such as learning and memory problems," Zoghbi said. "The mice only improved in what they had trained for."

When the researchers provided early training on memory tasks, the mice showed improvement on those tasks, and not others, when compared with Rett mice without training. The early intense training also delayed the appearance of memory and learning difficulties in these mice.

"We also discovered that the origin of this benefit arises from the repetitive activation of task-specific neurons," Achilly said.

Experiments revealed that task-specific neurons that are repeatedly activated during training develop more dendritic arbors or cellular projections that enable them to form and maintain neuronal circuits that enhance their functionality and delay symptom onset. Task-specific neurons of untrained animals, which showed normal progression of the condition, did not show changes in arborization.

"Our findings lead us to propose that newborn genetic testing for Rett syndrome, followed by prompt intensive training in the tasks that will be affected, could help the girls retain specific milestones and delay the onset of symptoms," Zoghbi said.

More information: Presymptomatic training mitigates functional deficits in a mouse model of Rett syndrome, *Nature* (2021). DOI: 10.1038/s41586-021-03369-7

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