NEWS

Brain stimulation could ease memory problems in Rett syndrome

BY **NICHOLETTE ZELIADT**

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Electrically stimulating a particular circuit in the brain improves learning and memory in a mouse model of Rett syndrome. The findings, detailed 14 October in *Nature*, suggest that some of the cognitive problems associated with the syndrome are reversible[1].

Cognitive impairment is a core feature of Rett syndrome, which primarily affects girls. The new findings raise the possibility that deep brain stimulation — an invasive technique that involves embedding electrodes in the brain — could ease cognitive problems in people with Rett syndrome and related conditions such as autism.

“Here’s a symptom that’s shared by so many individuals, no matter what the cause is,” says **Huda Zoghbi**, director of the Jan and Dan Duncan Neurological Research Institute at Texas Children’s Hospital in Houston. “We thought that if you can target the circuit that mediates that symptom, then you might discover an approach that could be applied to many of these disorders.” Zoghbi led the study along with **Jianrong Tang**, a neurophysiologist at the same institution.

Doctors currently use deep brain stimulation in people with Parkinson’s disease to ameliorate debilitating motor symptoms such as tremors and rigidity. Researchers are also testing the treatment in people with Alzheimer’s disease and depression.

“It’s a completely novel approach to targeting cognitive disorders,” says **Stuart Cobb**, a lecturer in neuroscience at the University of Glasgow, U.K., who was not involved in the study. “I think it’s very encouraging that it’s having quite a profound effect in Rett syndrome.”

Stimulating idea:

Zoghbi and her team surgically implanted electrodes in the brains of female mice missing a copy of the **MeCP2** gene, which is mutated in people with Rett syndrome. They positioned the electrodes to stimulate a nerve bundle that connects to the brain's memory center, the hippocampus.

The researchers stimulated the this nerve bundle in the mice for an hour each day for two weeks. Control mice missing MeCP2 were implanted with electrodes but did not receive stimulation.

Three weeks later, the mice that received the stimulation performed better than those that did not on learning and memory tests. In one test, for example, the treated mice were more likely to remember the context in which they received an unpleasant (but harmless) electric shock to their feet. They were also more efficient at finding a hidden platform in a pool of water. Contextual and spatial memory are both thought to require the hippocampus.

The researchers then took a closer look at the treatment's effects on neurons in awake and freely moving mice. No one knows exactly how deep brain stimulation works. It might alter the connections between neurons, or enhance or inhibit neuronal activity[2].

Zoghbi and her team found that in this case, the treatment enhances communication between neurons in the hippocampus — a process believed to underlie learning and memory. Using brain slices from the hippocampus, they found that the treatment also spurs the production of new neurons. It is still unclear, however, whether these brain changes are responsible for the altered behavior in the mice.

Short circuit: Stimulating a nerve bundle in mice modeling Rett syndrome enhances their ability to find a hidden platform in a pool of water.

Proof of principle:

The treatment did not improve other symptoms of Rett syndrome, such as movement problems, anxiety and social deficits. Nor did it trigger seizures or cause any other obvious side effects.

"These findings are quite remarkable," says **Mriganka Sur**, head of brain and cognitive sciences at the Massachusetts Institute of Technology in Cambridge, who was not involved in the study. "It's a powerful proof of principle for a circuit-based approach to the treatment of developmental disorders."

It's possible that stimulating other brain circuits might ease social and motor symptoms in Rett syndrome, Sur says. But he and others caution that the treatment needs more study before trying it in children, as it may have unforeseen effects on the developing brain.

"It's a big step to send your child to have deep brain stimulation," says **Irving Reti**, director of the

Brain Stimulation Program at the Johns Hopkins Hospital in Baltimore, who was not involved in the study. “But certainly this study is very exciting. It also says that if there’s some noninvasive way to stimulate the hippocampus, that could also be an effective treatment.”

REFERENCES:

1. Hao S. *et al. Nature* **526**, 430-434 (2015) **PubMed**
2. Miocinovic S. *et al. JAMA Neurol.* **70**, 163-171 (2013) **PubMed**