EFFECT OF STRIATAL DEEP BRAIN STIMULATION ON MOTOR DEFICITS IN RETT SYNDROME MICE

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Background: Deep brain stimulation (DBS) is a neuromodulatory approach involving electrical stimulation of subcortical brain structures to modulate neural function and network communication. Over decades, it has emerged as a revolutionary treatment option for essential tremor, Parkinson's disease, idiopathic dystonia, and severe obsessive-compulsive disorder. Rett Syndrome (RTT) is a neurodevelopmental disorder with cognitive, motor, sensory, emotional, and autonomic functional impairments. Most of the disease features were recapitulated in mice loss of MeCP2. We have previously showed that forniceal DBS improved hippocampus-related cognitive functions, hippocampal synaptic plasticity and neurogenesis in a RTT mouse model. Impaired motor function is another hallmark phenotype of RTT models, including deficits in motor coordination and motor skill learning, in which the striatum is highly involved. Here, we elucidated the effect of chronic bilateral DBS (130 Hz, 60 μs pulse duration) in the dorsomedial striatum (DMS) on the motor functions in RTT mice.

Materials/Methods: Animals were implanted with DBS electrodes in the DMS at the age of 31-32 weeks and recovered for at least one week before further experiments. Behavioral experiments including foot slip, open field, accelerating rotarod, wire hang, and pole test were designed to test the motor benefits of DMS-DBS. Ex vivo field potential recordings were conducted to measure the corticostriatal synaptic transmission and long-term potentiation (LTP) in this pathway.

Results: Compared to the sham-treated wild type (WT) littermates, sham-treated RTT mice exhibited significantly impaired performance in the accelerating rotarod, pole test, and wire hang test. However, DMS-DBS remarkably improved these deficits in RTT mice, without affecting the WT controls. In parallel, the diminished corticostriatal synaptic transmission and long-term potentiation (LTP) in this pathway were also restored by DMS-DBS in RTT mice.

Conclusions: These results might open a new opportunity to mitigate motor dysfunction in RTT through regulating the activity of motor circuitry by DBS. This project is funded by the Cockrell Family Foundation and NINDS R01 NS100738 (J.T.)